KREMLIN MEDICINE JOURNAL

Journal of research and practice

No. 1, 2019

Kremljovskaya Medicina. Clinichesky Vestnik
(Kremlin Medicine Journal) is peer-reviewed medical journal
The journal has been published since the 1993.

ISSN 1818-460X
Published 4 time per year

Publishing House:
Central State Medical Academy of Department of Presidential Affairs

Contacts information: E-mail: km@cgma.su
Web : www.kremlin-medicine.ru
Managing Editor: A.Yakushenkova
Adress: Marshala Timoshenko str., 19 -1 A. Moscow, 121359, Russia

CONTENTS
No 1 , 2019

ISSN 1818-460X

9 771818 460775 >

Doi 10.26269/rptj-w690

The opinion on the cystic pathology of the biliary tract, based on their own clinical experience

E.I. Brekhov, V.V. Kalinnikov, A.V.Sychev
Central State Medical Academy of Department of Presidential Affairs. Moscow, Russia

Abstract

The experience of studying the diagnosis and the surgical treatment of bile duct cysts by the domestic and foreign researchers is generalized. The authors point out that the clinical picture of this pathology is usually scanty and nonspecific. The main initial diagnostic method is ultrasonic echolocation. In most cases CT, NMR, ERCPG, etc are also necessary. However, the final diagnosis is established after histological examination. A radical method of the treatment is the surgical operation. The nature and extent of the intervention depends on the type of the cysts. Complete removal of the cystic formations with an adequate drainage for decompression of the biliary tract is the standard radical surgical treatment of this category of the patients. All these patients need subsequent periodic examinations to identify possible malignancy.

Key words: bile duct cysts, cystic pathology, biliary tract, choledochal cysts, endoscopic retrograde cholangiograms, malignancies in the cysts.

Cystic dilations of the gallbladder, involving extrahepatic and intrahepatic bile ducts are quite rare anomalies. Although this pathology was first documented by Vater and Ezler in 1723, the first complete clinical description of this defect was published in 1852 by Douglas [1, 2]. At that time, these changes were considered congenital McWhorter G.L.in 1924 [2]. In 1959 Alonso-Lej et al. published a detailed review of 94 cases of common bile duct cysts added two own cases. They classified the mentioned cysts into 3 types [3]. In 1977, Todani et al. divided the bile duct cysts into 5 types, adding 2 new types (types IV and V) [4]. The subtypes found in cholangiography were also described.

Now the classification is as follows:

- Type 1 (Figure 1) - Cystic sac or spindle-shaped dilatation of the common bile duct (most common type, 90-95% of cases).

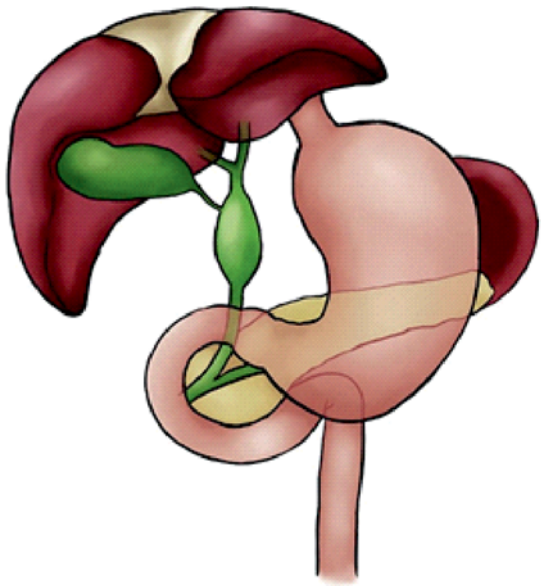


Fig. 1. Cyst of the bile duct of type 1.

- Type 1A is bag-shaped configuration, involves the entire common bile duct or most of it.
- Type 1B is bag-shaped configuration and involves a limited segment of the bile duct.
- Type 1C is more spindly in configuration and involves most or all of the hepatitis choledoch.

Type 2 (Figure 2) - Diverticulum of the common bile duct.

- Type 3 (Figure 3) -Hleedochocele, cystic dilatation of the distal part of the common bile duct.
- Type 4 (Figure 4) - Cystic sac or spindle-shaped dilatation of the common bile duct, associated with a cystic spindle-shaped or saccule dilatation of the intrahepatic bile ducts.
- Type 5 (Figure 5) - Cystic spindle-shaped, or saccule dilatation of intrahepatic bile ducts, associated with the normal common bile duct; can be associated with hepatic fibrosis (the association is referred to as Caroli's disease) [5].

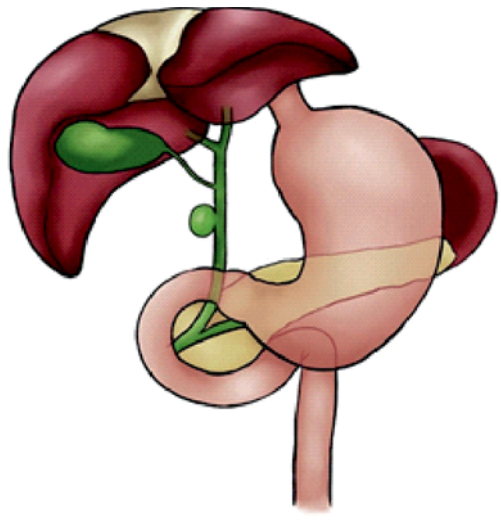


Fig. 2. Cyst of the bile duct of type 2.

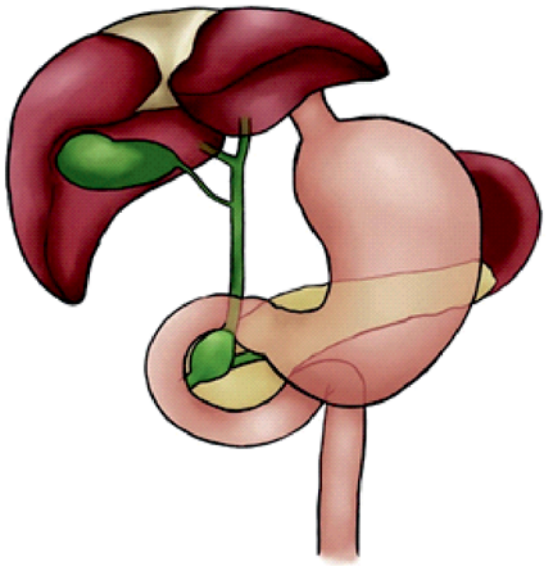


Fig. 3. Cyst of the bile duct of type 3.

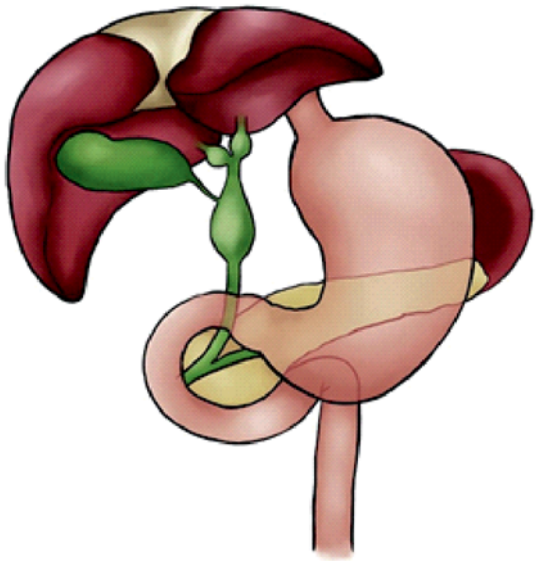


Fig. 4. Cyst of the bile duct of type 4.

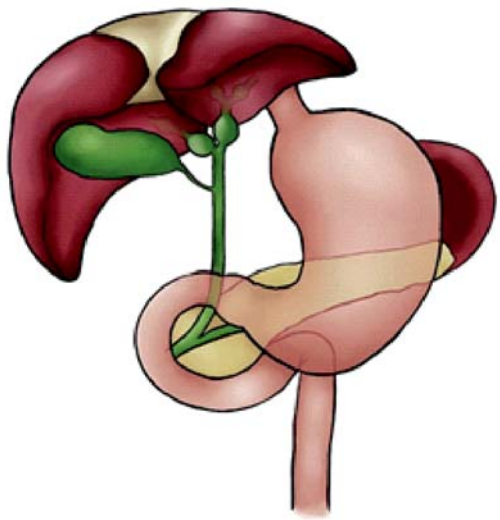


Fig. 5. Cyst of the bile duct of type 5.

Frequency: The prevalence of the bile cysts is from approximately 1 case in 13,000 to 1 in 2,000,000 people. The bile ducts are much more common in Asia than in Western countries [6]. Approximately 33-50% of the reports about this pathology come from Japan, where the frequency of these cysts is close to 1 case per 1000 population [7,8]. In an extensive survey published in 1980, Yamaguchi et al. examined 1,433 cases, 1,204 (more than two-thirds) of which were from Japan [9].

It is known that type 1 is the most frequent. In types 1 and 4, the ratio between women and men is approximately 4: 1, and in types 2, 3 and 5, cysts occur with equal frequency in both sexes.

Cysts of the bile ducts can be found in people of any age. Two-thirds of them are detected in children under 10 years [10,11,12,13,14,15,16]. About 20% of cysts are found in elderly people [17,18,19,20]. In rare cases, cysts of the common bile duct were found in prenatal ultrasonography during pregnancy 15 weeks, shortly after birth, the children underwent a surgical treatment [21].

Pathogenesis

The exact cause of the formation of the bile duct cysts remains unclear. Many authors believe that they are congenital, because most cysts are diagnosed in infants and children. However, due to the fact that approximately 20% of hepatitis choledochal cysts are diagnosed in adults, including elderly patients, allowed to assume several more development mechanisms [14,17,22,23,24]:

- Weakness of the bile duct wall [6,25,26].
- Development of the distal department of choledochus [27].
- A combination of the duct obstruction and weakness of the wall [28].
- Reflux of pancreatic enzymes into the common bile duct, a secondary anomaly of the pancreatobiliary compound [18,29,30,31,32,33].

In 1969, Babbitt and colleagues, after analyzing the cholangiograms of the patients with the common bile duct cysts, found in most of them an anomaly of the pancreatobiliary pancreatobiliary communication in which the pancreatic duct was more proximal. They hypothesized that such an anomaly caused reflux of pancreatic secretion in holedoch, as the pressure in the pancreatic duct was higher than the pressure in the bile duct. It was concluded that the classical triad: fever, abdominal pain, and jaundice occurred due to the recurrent cholangitis attacks. As a result of inflammation, the choledochal wall was damaged, followed by healing and thickening, which led to the obstruction in the distal part of the bile duct [29].

In 1977, Spitz supported the concept of distal obstruction of the common bile duct as the cause of the formation of the choledochal cysts, demonstrating the

dilatation of the bile duct in lambs obtained by ligating the duct near the confluence of the duodenum [27]. The same experiment was performed to simulate the dilatation of the bile duct in mature sheep.

In 1974, Kato et al. were the first researchers who created the cyst of the common bile duct in experimental animals by transpupillary curettage of the bile duct and subsequent, 3-4 days later, ligation of the ampulla of the falcon papilla [28].

In 1984, Todani et al. performed an analysis of the endoscopic retrograde cholangiograms (cholangiopancreatograms) and confirmed this anomaly in the common canal [33]. Cystic lesions were found in most patients. There are other authors' reports of the same research results [18,30,31,34,35]. Reflux pancreatic enzymes in the common bile duct can occur quite early, even in embryonic period, leading to the damage of the duct wall. The distal part of the choledoch is the most vulnerable, and with repeated injuries, its stenosis may occur.

Experimental support of this concept was reported by Kato et al. in 1974. They imposed an anastomosis between the main pancreatic duct and the gallbladder in dogs. Within 9 days after the application of the anastomosis, all the animals studied had different degrees of dilatation of the common bile duct, with edematic changes in its wall. They concluded that proteolytic enzymes were responsible for this damage [28].

Miyano et al. (1981 and 1984) created an experimental model of an abnormal choledochocampanic compound, creating an end-to-side choledochocinchoracic anastomosis in puppies. They successfully reproduced the dilation of choledoch in all experimental animals without exception [31,32].

All these theories are applicable to types 1, 3 and 4, but they cannot be used to explain 2 and 5 types of the common bile duct cysts in which the common bile duct is normal. Perhaps genetic factors play a major role [6,8,23]. Thus, at present there are two most well-founded theories - reflux of pancreatic enzymes into the common bile duct, with an abnormal pancreatobiliary compound and obstruction of the distal part of the choledochus [36].

Pathological features

The size of the cyst of the common bile duct of type 1 is very variable [6,11,12,17,19,34,37,38]. The volume of the cyst can reach up to several hundred milliliters of bile with pancreatic enzymes. The thickness of the cyst wall is also variable.

Intrahepatic cysts can be fusiform or saccular and are connected with the common bile duct. Suspension and stones are sometimes present within the cyst [6,8]. The bile duct, distal to the cyst, is usually stenosed. The liver can have a different level of fibrosis or cirrhosis with portal hypertension. A histological examination of the wall of the cyst of the common bile duct revealed a dense fibrous connective tissue with the inflammation and the formation of mucosal and submucous layers.

The inflammation is much less developed in young patients than in older patients [8,35,39,40]. The cyst is lined with a thin, fragmented cover, but not the normal lining of the biliary tract.

The inflammatory process with the intrahepatic cyst location is more frequent than in the extrahepatic cyst location.

Histological examination: the signs of chronic inflammation are observed in the wall of the cyst. It is thin, fibrous, and often devoid of a true epithelial surface, although it can be lined with a low columnar epithelium. It is noted that the infants can develop a complete obstruction of the distal part of the common bile duct as a result of an acute or chronic inflammation. In the liver, there may be intraductal fibrosis and portal swelling. Cirrhosis like changes may occur in adults with chronical illness. The most unpleasant histological finding is cholangiocarcinoma.

Cysts of common bile duct and malignancy

The possibility of cancer in the wall of the cyst of the common bile duct or in the remaining gall-stone after complete cyst resection is a recognized fact. Malignant development is believed to be the result of a prolonged stagnation of the bile and chronic inflammation with metaplasia. Typical malignant development - adenoskvamozny cancer or small cell cancer.

Malignancies in the cysts of the common bile duct can undergo the distal section of the choledochus, more than half the cases of the cyst wall (even after successful internal drainage), or intrahepatic bile ducts. The complete cyst resection does not prevent the risk of malignant degeneration in the remaining bile ducts. The risk of cancer increases with the age of the patient [4,14,41,42,43,44,45]. So the detection of malignancy in the resected cyst is 0.7% in patients operated up to 10 years of age; 6.8% in patients operated in 11-20 years; and 14.3% in patients operated after 20 years. Malignancy can occur many years after the removal of the cyst and develop in areas of bilious tree distant from the cyst, for example, the gallbladder.

Any type of the cyst can be prone to malignant transformation, but the greatest prevalence of the oncological process is observed in types 1, 4, 5. The increased risk of malignancy of the bile tree, even after radical surgery, requires monitoring of such patients.

Lethality / Complicated course: variants of complicated course associated with the bile duct cysts depend on the age of the patients. Infants and children may develop pancreatitis, cholangitis and signs of hepatocellular injury. In adults with subclinical duct inflamma-

tion and bile congestion that may have been present for many years, one or more severe complications such as pancreatitis, choledocholithiasis, cholangitis, intrahepatic abscesses, portal hypertension, cirrhosis may occur. Cholangiocarcinoma is the most dangerous complication of choledoch cysts. Lethality varies depending on the level of the complication.

Prenatal diagnosis

In connection with the development of prenatal ultrasound, an increasing number of the common bile cysts in the fetus was reported: Hammada, 1998; Lipset, 1994; Marchildon, 1988; Mackenzie, 2001; Shamberger, 1995 [17,21,46,47,48,49]. Incomplete obstruction of a large cyst is one of the typical clinical manifestations in newborns and infants [50]. The earliest cyst of the common bile duct reported is found in the fetus during gestation of 15 weeks, which may correspond to the time of formation of the pancreatic enzymes.

Prenatal detection of the cystic structure in the extrahepatic sections of the bile duct suggests a diagnosis of choledochal cyst, after which the diagnosis must be verified by successive ultrasound examinations. In most surgical clinics, they prefer to remove the cyst shortly after birth. Within a few weeks, it is necessary to stabilize the child's condition and carry out the necessary examinations. The surgical treatment in newborns has shown that it is technically simple and well tolerated by the patients.

Clinical manifestations

Patients with choledochal cysts are divided into two groups according tot their age [12,14,17,39,40].

The first group includes infants younger than 1 year with hepatomegaly or without an obvious increase in liver size, with obstructive jaundice and acholic feces. This clinical picture is indistinguishable from that which occurs with biliary atresia, in the absence of palpation of the formations (cysts) of the right half of the abdominal cavity. The presence of cystic formation may be suspected during clinical examination and is confirmed on ultrasonography, only thus the diagnosis of the cyst choledoch is competent.

In 1995, Todani et al. found that 26 out of 28 infants with a clinical picture younger than 1 year had cysts of choledoch, whereas only 3 out of 8 children aged 13-24 months had that pathology [40]. Other symptoms, such as vomiting, fever, and abdominal pain with hyperamilazemia were not often detected [19]. In infants diagnosed with a common bile duct cyst in the prenatal period, jaundice often didn't not appear until 1-3 weeks after birth [51,52].

In contrast, the second group, infants over 1 year old, with the so-called adult form of the cyst of the common bile duct, generally had 1 or more components of the classical triad: pain, jaundice, and palpation of the cyst. The entire triad is present in less than 30% of patients [14]. Jaundice and intermittent fever were often associated with an undefined abdominal pain. The pain was associated with developing cholangitis and moderate chronic pancreatitis.

Unidentified cysts of the common bile duct can lead to choledocholithiasis, cirrhosis of the liver with portal hypertension, rupture of the cyst, and cancer of the biliary tract.

Laboratory tests that may be useful for diagnosis and preoperative assessment of patients with bile duct cysts include: direct bilirubin, alkaline phosphatase, serum glutamine oxalate transaminase (SGOT), serum glutamine pyruvate transaminase (SGPT), gamma-glutamyl transferase (GGT), a coagulation system, a clinical blood test.

None of these tests is determinative for the diagnosis of the common bile duct cyst.

Instrumental methods of research.

1. Ultrasonography is the best initial study, allowing to detect the changes in the bile duct and liver. In newborns, this may be the only method of investigation. In the antenatal period Sgro and colleagues detected Caroli's disease (2004) only with the help of ultrasound [23].

2. CT and NMR help to outline the anatomy of the lesion and the structures closest to it, and can also determine the presence of an enlargement of the intrahepatic part of the bile ducts. Adult patients may benefit from CT scans in combination with cholangiography.

3. Radiography with cholangiography, when giving contrast per os or intravenous administration, is of limited use and is considered obsolete.

4. Scintigraphy with 99Tc diisopropyl iminodiacetate can show complete obstruction of the distal bile duct [14,17].

5. Endoscopic retrograde cholangiopancreatography (ERCP) is the choice in older patients. In experienced hands, ERCP can be performed with a high degree of success, even in infants. Successfully implemented ERCPH objectively demonstrates the anatomical relationship of the pancreatic-biliary compound [4,11,33,34]. Percutaneous transhepatic cholangiography can also be used for indications.

6. The method of magnetic resonance with cholangiopancreatography has more diagnostic value compare to cholangiography and ERCP in patients with choledochal and biliary ducts in general [31,53,54,55,56].

Treatment

The basis of treatment is the surgical removal of the cyst with subsequent decompression of the biliary tract, except type 5 (with numerous intrahepatic formations). The tactic of the surgical treatment of patients with the

cysts of the common bile duct has developed most during the last three decades. At present, a complete resection of the cyst and the gallbladder has become the main method of choice. Other operations, such as cystoduodenostomy or cystojunostomy, cannot be considered radical, besides they have a high risk of complications and the greatest potential risk of malignant degeneration in the residual cyst. Even after a complete resection of the cyst, sporadic cases of cancer in the remaining gall bladder occur.

In the past, aspiration external drainage was used, which is a simple and quick procedure, although very painful. However, external drainage of the gall bladder was often accompanied by numerous complications, including recurrent cholangitis and biliary fistula. Mortality rates were also high [6,14,17].

Internal drainage: cystoduodenoanastomosis or cystojunoanastomosis, also used in the past. In these variants of operations, there was free reflux of pancreatic enzymes in the cyst through an abnormal pancreatobiliary compound that led to the development of cholangitis, the formation of anastomotic stricture, and the possibility of cancer of the biliary tract. Among the patients undergoing cystoduodenoanastomosis or cystojunoanastomosis, 60% remained on symptomatic treatment, and 40% required re-operation [57,58].

Complete removal of the cyst in types 1, 2 and 4, accompanied by the reconstruction of gall bladder with hepatocojunostomy (method Roux) is widespread, as the preferred method in the treatment of cysts common bile duct. This procedure involves resection of the distal choledochus, which blocks the reflux of pancreatic enzymes and reduces the risk of malignancy of the bile ducts.

Complete removal of the cyst is possible in infants and young children. In adult patients with recurrent cholangitis and inflammation, resection of the anterolateral part of the cyst is indicated, leaving the wall adjacent to the portal vein. This technique is also the most promising in patients who have undergone cystoenterostomy and require a second operation, due to repeated attacks of cholangitis.

Intraoperative cholangiography is performed by puncturing the cyst or gall bladder. It determines the exact anatomy of the cyst of the common bile duct and its relationship to the pancreas. Usually cholecystectomy is performed simultaneously.

Biliary reconstructions can most often be performed with hepatitis-neurastomy on Roux, as high as possible [8,11,39,60]. However, some authors, including Raffensperger and Shamberger, used the jejunum segment to prevent reflux. This idea was not accepted by everyone. Installation of any stands is usually not shown [49,61,62,63].

With type 2 cysts of the common bile duct, a simple removal of the diverticulum with ductoplasty for the reconstruction of the common bile duct is all that is required. Laparoscopic removal was successfully performed with this rather rare type of cyst in 2000 [64].

With type 3 cysts of the common bile duct, duodenotomy with separate drainage of the biliary and pancreatic ducts directly into the duodenum is shown [34,60,65].

In patients with type 4 cysts of the common bile duct with intrahepatic cysts, each case should be evaluated individually, necessarily adequate drainage of the gallbladder. Resection of the enlarged extrahepatic bile ducts should be performed to the liver gates, followed by hepatitis-yoanastomosis at the level of the liver gates, can provide adequate outflow of the bile and effective decompression of the intrahepatic cysts. If the intrahepatic cysts are localized in a limited part of the liver, partial liver resection is indicated [18,66,67].

At type 5 of the cyst of the common bile duct, patients with a limited spread of cysts are shown hepatic lobectomy. If the disease is disseminated, affecting both liver lobes, the treatment is palliative or, in exceptional cases, liver transplantation may be required [14,60,68,69,70].

Complications after the surgical treatment were mainly observed in patients with types 1, 4 and 5 cysts. Mortality and relapse of the disease are low after surgical removal of cystic formations, in comparison with the methods of their internal drainage.

Postoperative complications:

1. Holangite.
2. Formation of stones.
3. Constriction of anastomosis.
4. Dilation of intrahepatic bile ducts, especially with 4 and 5 types of cysts of the common bile duct.
5. Malignancy.

We have been studying this problem for more than 30 years, since the first time we encountered cystic formation of extrahepatic bile ducts. During the planned operation for chronic calculous cholecystitis, a local expansion of hepatiko choledocha was detected, conditionally, in the region of the confluence of the vesicular duct. This education was initially taken for the region of the "neck" of the gallbladder and the surgeon, being sure that he had produced only cholecystectomy, resected part of the extrahepatic bile duct. With intraoperative cholangiography (the terminal part of the supraduodenal department of choledocha was taken for the stump of the vesicular duct), it became clear what happened. In the operating room, Professor E.I. Brekhov. Taking into account what has happened, reconstruction to Roux. The postoperative period proceeded without complications. The patient was discharged on the 12th

day after the operation. Diagnosis at discharge: Cyst of common bile duct, type 1B. With a histological examination, the diagnosis of the cyst is confirmed. Later it was observed for 5 years. Data for the stricture of anastomosis and malignancy were not revealed.

In the following, about 23 cysts of the bile ducts were performed. Of these, with the established diagnosis of the cyst of the bile duct of type 1, 8 patients were routinely operated. All of them were subjected to a resection of the cystic-altered extrahepatic bile ducts and hepatic neuronostomy according to Roux.

Also, the patient with the diagnosis was prepared for the operation in a planned order: Peptic ulcer of duodenal ulcer, complicated by stenosis of the outlet stomach. During the preoperative examination, in addition to the above pathology, the hepaticocholedochus cyst, a rounded shape, 5.0 cm in diameter was detected. A simultaneous operation was performed: 2/3 resection of the stomach according to Balfour. Cholecystectomy. Resection of hepatitis choledoch. Hepatikojannoanastomoz end-to-side. The cystic-altered part of the hepaticocholedochus is resected proximally by 1.0 cm below the bifurcation of the right and left hepatic ducts, and in the distal slightly above the border of the supraduodenal and retro-duodenal parts. The distal part is sewn with a double-suture. Gastroentero and hepatitis yunoanastomoz is divided by a mechanical seam.

In 12 cases, as in our first observation, the cysts of extrahepatic bile ducts are diagnosed intraoperatively. Resections of hepatiko-choledocha with cystic lesions of various volumes were performed. In 4 cases, a hepatopojunostomia was performed according to Roux, and in 8, hepatitis yunoanastomosis with entero-entero anastomosis was applied.

Two cases require a separate mention, due to the fact that the diagnosis of cysts was not performed intraoperatively and the situation is regarded as iatrogenic technical error.

In the first observation, when performing a cholecystectomy, a significant part of the hepatoc choledocha was resected, in the proximal part above the fusion of the right and left hepatic ducts. In connection with the extent of the defeat, a reconstructive-reconstructive operation was impossible. The external drainage of both hepatic ducts has been performed, the safety drainage has been placed in the abdominal cavity. In the future, the safety drainage was removed and the patient was discharged for outpatient treatment. Repeated hospitalization after 4 months. Reconstructive surgery was performed anastomoz in Roux.

In the other case, from the second day after the planned laparoscopic cholecystectomy, the progressive icterus of the skin and the sclera were noted. The RCCP was performed, in which the filling of the terminal part of the common bile duct with filling of the contrast medium was detected during 4.5 cm, there was no further contrasting. Iatrogenic trauma of extrahepatic bile ducts is suspected. Transhepatic drainage of the biliary tract and cholangiography were performed, which showed contrasting intrahepatic, right and left hepatic bile ducts. The filling of the common bile duct with contrast medium is about 1.0 cm. The patient was discharged from the hospital and two months later she was hospitalized again for a reconstructive-reconstructive operation.

Hepatic fusion on the Roux was made. The postoperative period proceeded without complications.

In both cases, morphological examination was used to diagnose cysts (type 1) in the resected parts of the hepaticocholedochus.

Thus, based on the literature and our own research, we can formulate the following conclusions:

1. Patients with suspected cystic changes in the bile duct require a thorough and comprehensive study of the biliopancreato-duodenal region.

2. To resolve the issue of surgical (operative) treatment, it is necessary to determine the nature and type of cystic lesions, clear topographic and anatomical relationships with neighboring organs.

3. The operation of "choice" for cysts of the first type is a resection of hepatitis choledoch with hepatitis-inhurations according to Roux. However, based on our observation with exclusive combined pathology, other variants of reconstructions are possible.

4. In emergency situations, when detecting both the cysts and iatrogenic intraoperatively, it is possible to make simpler decisions that do not complicate the situation, including the choice of anastomosing and external drainage.

5. In spite of the fact that the results of surgical treatment with the pathological changes under consideration are, as a rule, good, the risk of malignancy takes place. Therefore, all patients in this category should be under observation for at least 5 years.

Summarizing the above, it can be stated that the complete removal of the cyst with adequate drainage for decompression of the biliary tract is the standard radical surgical treatment of this category of the patients. All these patients need subsequent periodic examinations for the purpose of early detection of complications and possible malignancy.

Reference

1. *Chernousov A.F. et al: Surgical treatment of cystic diseases of bile ducts. J. Surgery named after N.I.Pirogov/Khirurgiya. Zhurnal imeni N.I.Pirogova/. 2016; 1: 85-92.*

2. *Milonov O.B., Gureeva H.F.: Congenital cysts of the bile duct. J.Surgery named after N.I.Pirogov/Khirurgiya. Zhurnal imeni N.I.Pirogova/. 1982; 1: 108-114.*

3. *Alonso-Lej F., Revor W.B., Passango D.J.: Congenital choledochal cyst, with a report of 2, and an analysis of 94 cases. Surg. Gynecol. Obstet. 1959; 108: 1-30.*

4. Todani T., Watanabe Y., Narusue M., et al.: Congenital bile duct cysts: Classification, operative procedures, and review of thirty-seven cases including cancer arising from choledochal cyst. Am. J. Surg. 1977 Aug.; 134(2): 263-269.

5. Todani T., Watanabe Y., Toki A., Morotomi Y.: Classification of congenital biliary cystic disease: special reference to type Ic and IV A cycts with primary ductal structure. J. Hepatobilairy Pancreat. Surg. 2003; 10: 340-344.

6. Flanigan P.D.: Biliary cysts. Ann. Surg. 1975 Nov.; 182(5): 635-43.

7. Miyano T., Yamataka A., Kato Y.: Choledochal cysts: special emphasis on the usefulness of intraoperative endoscopy. J Pediatr. Surg. 1995 Mar.; 30(3): 482-484.

8. Miyano T., Yamataka A., Kato Y., et al.: Hepaticoenterostomy after excision of choledochal cyst in children: a 30-year experience with 180 cases. J. Pediatr. Surg. 1996 Oct.; 31(10): 1417-1421.

9. Yamaguchi M.: Congenital choledochal cyst. Analysis of 1433 patients in the Japanese literature. Am. J. Surg. 1980 Nov.; 140(5): 653-657.

10. Edil B.H., Cameron J.L., Reddy S., Lum Y., Lipsett P.A., Nathan H., Pawlik T.M., Choti M.A., Wolfgang C.L., Schulick R.D.: Chole dochal cyst disease in children and adults: a 30-year single-institutional experience. J. Am. Coll. Surg. 2008; 206: 1000-1008.

11. Kasai M., Asakura Y., Taira Y.: Surgical treatment of choledochal cyst. Ann. Surg. 1970 Nov.; 172(5): 844-851.

12. Katyal D., Lees G.M.: Choledochal cysts: a retrospective review of 28 patients and a review of the literature. Can. J. Surg. 1992 Dec.; 35(6): 584-588.

13. Morozov D.A., Gusev A.A., Pimenova E.S.: Bile Duct Cysts: Modern Aspects of Surgical Treatment and Clinical Observation of a Rare Case. Voprosy sovremennoi pediatrii-Current Pediatrics 2015; 14(3): 412-415.

14. O'Neill J.A.: Choledochal cyst. Curr. Probl. Surg. 1992 Jun.; 29(6): 361-410.

15. Soreide K., Korner H., Havnen J., Soreide J.A.: Bile duct cysts in adults. Brit. J. Surg. 2004; 91: 1538-1548.

16. Visser B.C., Suh I., Way L.W., Kang S.M.: Congenital choledohal cysts in adults. Arch. Surg. 2004; 139: 855-862.

17. Lipsett P.A., Pitt H.A., Colombani P.M., et al.: Choledochal cyst disease. A changing pattern of presentation. Ann. Surg. 1994 Nov.; 220(5): 644-652.

18. Okada A., Nakamura T., Higaki J., et al.: Congenital dilatation of the bile duct in 100 instances and its relationship with anomalous junction. Surg. Gynecol. Obstet. 1990 Oct.; 171(4): 291-298.

19. Saing H., Tam P.K., Lee J.M., Pe-Nyun: Surgical management of choledochal cysts: a review of 60 cases. J. Pediatr. Surg. 1985 Aug.; 20(4): 443-448.

20. Suita S., Shono K., Kinugasa Y., et al.: Influence of age on the presentation and outcome of choledochal cyst. J. Pediatr. Surg. 1999 Dec.; 34(12): 1765-1768.

21. Howell C.G., Templeton J.M., Weiner S., et al.: Antenatal diagnosis and early surgery for choledochal cyst. J. Pediatr. Surg. 1983 Aug.; 18(4): 387-393.

22. Tadokoro H., Takase M.: Recent advances in choledochal cysts. Open J. Gastroenterol. 2012; 2: 145-154.

23. Yamaguchi M., Sakurai M., Takeuchi S., Awazu S.: Observation of cystic dilatation of the common bile duct by ultrasonography. J. Pediatr. Surg. 1980 Apr.; 15(2): 207-210.

24. Yamashiro Y., Miyano T., Suruga K., et al.: Experimental study of the pathogenesis of choledochal cyst and pancreatitis, with special reference to the role of bile acids and pancreatic enzymes in the anomalous choledocho-pancreatico ductal junction. J. Pediatr. Gastroenterol Nutr. 1984 Nov.; 3(5): 721-727.

25. Babbitt D.P., Starshak R.J., Clemett A.R.: Choledochal cyst: a concept of etiology. Am. J. Roentgenol. Radium. Ther. Nucl. Med. 1973 Sep.; 119(1): 57-62.

26. Bismuth H., Krissat J.: Choledochal cystic malignancies. Ann. Oncol. 1999; 10 (Suppl. 4): 94-98.

27. Spitz L.: Experimental production of cystic dilatation of the common bile duct in neonatal lambs. J. Pediatr. Surg. 1977 Feb.; 12(1): 39-42.

28. Kato T., Asakura Y., Kasai M.: An attempt to produce choledochal cyst in puppies. J. Pediatr. Surg. 1974 Aug.; 9(4): 509-513.

29. Babbitt D.P.: Congenital choledochal cysts: new etiological concept based on anomalous relationships of the common bile duct and pancreatic bulb. Ann. Radiol. (Paris) 1969; 12(3): 231-240.

30. Kato T., Hebiguchi T., Matsuda K., Yoshino H.: Action of pancreatic juice on the bile duct: pathogenesis of congenital choledochal cyst. J. Pediatr. Surg. 1981 Apr.; 16(2): 146-151.

31. Miyano T., Suruga K., Suda K.: Abnormal choledocho-pancreatico ductal junction related to the etiology of infantile obstructive jaundice diseases. J. Pediatr. Surg. 1979 Feb.; 14(1): 16-26.

32. Miyano T., Suruga K., Suda K.: Choledocho-pancreatic end to side anastomosis in dog as an experimental model of choledocho-pancreatic long common channel disorders. Jpn. J. Pediatr. Surg. 1981; 13: 525-531.

33. Todani T., Watanabe Y., Fujii T., Uemura S.: Anomalous arrangement of the pancreatobiliary ductal system in patients with a choledochal cyst. Am. J. Surg. 1984 May; 147(5): 672-676.

34. Jona J.Z., Babbitt D.P., Starshak R.J., et al.: Anatomic observations and etiologic and surgical considerations in choledochal cyst. J. Pediatr. Surg. 1979 Jun.; 14(3): 315-320.

35. Oguchi Y., Okada A., Nakamura T., et al.: Histopathologic studies of congenital dilatation of the bile duct as related to an anomalous junction of the pancreaticobiliary ductal system: clinical and experimental studies. Surgery 1988 Feb.; 103(2): 168-173.

36. Yamataka A., Segawa O., Kobayashi H., et al.: Intraoperative pancreatoscopy for pancreatic duct stone debris distal to the common channel in choledochal cyst. J. Pediatr. Surg. 2000 Jan.; 35(1): 1-4.

37. Postema R.R., Hazebroek F.W.: Choledochal cysts in children: a review of 28 years of treatment in a Dutch children's hospital. Eur. J. Surg. 1999 Dec.; 165(12): 1159-1161.

38. Todani T., Watanabe Y., Urushihara N., et al.: Biliary complications after excisional procedure for choledochal cyst. J. Pediatr. Surg. 1995 Mar.; 30(3): 478-481.

39. Raffensperger J.G.: Swenson's Pediatric Surgery. 5th ed. Norwalk, Conn: Appleton & Lange; 1990:665.

40. Todani T., Urushihara N., Morotomi Y., et al.: Characteristics of choledochal cysts in neonates and early infants. Eur. J. Pediatr. Surg. 1995 Jun.; 5(3): 143-145.

41. Imazu M., Iwai N., Tokiwa K., et al.: Factors of biliary carcinogenesis in choledochal cysts. Eur. J. Pediatr. Surg. 2001 Feb.; 11(1): 24-27.

42. Iwai N., Deguchi E., Yanagihara J., et al.: Cancer arising in a choledochal cyst in a 12-year-old girl. J. Pediatr. Surg. 1990 Dec.; 25(12): 1261-1263.

43. Todani T., Tabuchi K., Watanabe Y., Kobayashi T.: Carcinoma arising in the wall of congenital bile duct cysts. Cancer 1979 Sep.; 44(3): 1134-1141.

44. Todani T., Watanabe Y., Toki A., Urushihara N.: Carcinoma related to choledochal cysts with internal drainage operations. Surg. Gynecol. Obstet. 1987 Jan.; 164(1): 61-64.

45. Watanabe Y., Toki A., Todani T.: Bile duct cancer developed after cyst excision for choledochal cyst. J. Hepatobiliary Pancreat. Surg. 1999; 6(3): 207-212.

46. Hamada Y., Tanano A., Sato M., et al.: Rapid enlargement of a choledochal cyst: antenatal diagnosis and delayed primary excision. Pediatr. Surg. Int. 1998 Jul.; 13(5-6): 419-421.

47. Mackenzie T.C., Howell L.J., Flake A.W., Adzick N.S.: The management of prenatally diagnosed choledochal cysts. J. Pediatr. Surg. 2001 Aug.; 36(8): 1241-1243.

48. Marchildon M.B.: Antenatal diagnosis of choledochal cyst: the first four cases. Pediatr. Surg. Int. 1988; 3: 431-436.

49. *Shamberger R.C, Lund D.P., Lillehei C.W., Hendren W.H. 3rd: Interposed jejunal segment with nipple valve to prevent reflux in biliary reconstruction. J. Am. Coll. Surg. 1995 Jan.; 180(1):10-15.*

50. *Komuro H., Makino S., Tahara K.: Choledochal cyst associated with duodenal obstruction. J. Pediatr. Surg. 2000 Aug.; 35(8): 1259-1262.*

51. *Ono S., Tokiwa K., Aoi S., et al.: A bleeding tendency as the first symptom of a choledochal cyst. Pediatr. Surg. Int. 2000; 16(1-2): 111-112.*

52. *Patel S., Sterkin L., Donahue P.E., Young S.: Congenital cyst of common bile duct: an unusual cause of obstructive jaundice. Surgery 1991 Mar.; 109(3 Pt.1): 333-335.*

53. *Frampas E., Moussaly F., Leaute F., et al.: [MR cholangiopancreatography in choledochal cysts]. J. Radiol. 1999 Dec.; 80(12): 1659-1663.*

54. *Fulcher A.S., Turner M.A.: MR cholangiopancreatography. Radiol. Clin. North Am. 2002; 40: 1363-1376.*

55. *Kim S.H., Lim J.H., Yoon H.K., et al.: Choledochal cyst: comparison of MR and conventional cholangiography. Clin. Radiol. 2000 May; 55(5): 378-383.*

56. *Yamataka A., Ohshiro K., Okada Y., et al.: Complications after cyst excision with hepaticoenterostomy for choledochal cysts and their surgical management in children versus adults. J. Pediatr. Surg. 1997 Jul.; 32(7): 1097-1102.*

57. *Chijiiwa K., Koga A.: Surgical management and long-term follow-up of patients with choledochal cysts. Am. J. Surg. 1993 Feb.; 165(2): 238-242.*

58. *Chijiiwa K., Tanaka M.: Late complications after excisional operation in patients with choledochal cyst. J. Am. Coll. Surg. 1994 Aug.; 179(2): 139-44.*

59. *Hata Y., Sasaki F., Takahashi H, et al.: Surgical treatment of congenital biliary dilatation associated with pancreaticobiliary maljunction. Surg. Gynecol. Obstet. 1993 Jun.; 176(6): 581-587.*

60. *Joseph V.T.: Surgical techniques and long-term results in the treatment of choledochal cyst. J. Pediatr. Surg. 1990 Jul.; 25(7): 782-787.*

61. *Cosentino C.M., Luck S.R., Raffensperger JG, Reynolds M: Choledochal duct cyst: resection with physiologic reconstruction. Surgery 1992 Oct.; 112(4): 740-747; discussion 747-748.*

62. *Fu M., Wang Y., Zhang J.: Evolution in the treatment of choledochus cyst. J. Pediatr. Surg. 2000 Sep.; 35(9): 1344-1347.*

63. *Reynolds M., Luck S.R., Raffensperger J.G.: The valved conduit prevents ascending cholangitis: a follow-up. J. Pediatr. Surg. 1985 Dec.; 20(6): 696-702.*

64. *Liu D.C., Rodriguez J.A., Meric F., Geiger J.L.: Laparoscopic excision of a rare type II choledochal cyst: case report and review of the literature. J. Pediatr. Surg. 2000 Jul.; 35(7): 1117-1119.*

65. *Maning P., Polley T., Oldam K.: Choledochocele: an unusual form of choledochal cyst. Pediatr. Surg. Int. 1990; 5: 22-26.*

66. *Ohi R., Koike N., Matsumoto Y., et al.: Changes of intrahepatic bile duct dilatation after surgery for congenital dilatation of the bile duct. J. Pediatr. Surg. 1985 Apr.; 20(2): 138-142.*

67. *Ohi R., Yaoita S., Kamiyama T., et al.: Surgical treatment of congenital dilatation of the bile duct with special reference to late complications after total excisional operation. J. Pediatr. Surg. 1990 Jun.; 25(6): 613-617.*

68. *Todani T., Narusue M., Watanabe Y., et al.: Management of congenital choledochal cyst with intrahepatic involvement. Ann. Surg. 1978 Mar.; 187(3): 272-280.*

69. *Todani T., Watanabe Y., Fujii T., et al.: Congenital choledochal cyst with intrahepatic involvement. Arch. Surg. 1984 Sep.; 119(9): 1038-1043.*

70. *Jilly J.R.: Total excision of choledochal cyst. Surg. Gynecol. Obstet. 1978 Feb.; 146(2): 254-256.*

Corresponding author
Valentin V. Kalinnikov
unmc-surgery@yandex.ru

No conflict of interest stated.

Information about authors

Eugene I. Brekhov, head of Chair of Surgery of Central State Medical Academy of Department of Presidential Affairs. St. Marshala Timoshenko 19, 1 A, Moscow 121359, Russia

Valentin V. Kalinnikov, professor of Chair of Surgery of Central State Medical Academy of Department of Presidential Affairs. Marshala Timoshenko str., 19, 1 A, Moscow 121359, Russia.

Andrew V. Sychev assistant professor of Chair of Surgery of Central State Medical Academy of Department of Presidential Affairs. St. Marshala Timoshenko 19, 1 A, Moscow 121359, Russia

doi 10.26269/yakp-9e49

The practical application of modern guidelines for the diagnosis and treatment of exocrine pancreatic insufficiency in patients with chronic pancreatitis

O.N. Minushkin, L.V. Maslovsky, A.E.Evsikov , A.M. Chebotareva
Central State Medical Academy of Department of Presidential Affairs , Moscow, Russia

Abstract

The article presents an overview of current European and Russian guidelines of the diagnosis and management of exocrine pancreatic insufficiency in patients with chronic pancreatitis. The results of our own comparative studies on the treatment of pancreatic enzyme insufficiency in 55 patients treated with enzyme replacement therapy with adequate and low doses confirm the advisability of using the recommended doses of enzyme replacement therapy (ERT) (micronized polyenzyme drugs), since not only the reduction of the clinical signs are observed, but also the normalization of the nutritional status. The results of the study indicate that the optimal way to assess the effectiveness of the ERT is to normalize the anthropometric and biochemical parameters of the nutritional status.

Key words: chronic pancreatitis; exocrine pancreatic insufficiency; nutritional status; treatment.

In February 2017, terms of the Russian consensus on the diagnosis and treatment of chronic pancreatitis were presented. Purposes of this consensus document, prepared on initiative of the Russian " Pancreatic Club " were the identification and consolidation of leading domestic specialists' views (gastroenterologists, surgeons, pediatricians) on current diagnosis and treatment issues of chronic pancreatitis (CP) [1].

In March 2017 Paneuropean clinical guidelines for the diagnosis and treatment of chronic pancreatitis, based on the principles of evidence-based medicine, were published. Twelve interdisciplinary groups presented systematic reviews of the scientific literature describing etiology of CP, instrumental diagnostics using visualization methods, diagnostics of exocrine pancreatic insufficiency (EPI), surgical, medical and endoscopic treatment; treatment of pancreatic pseudocysts, pancreatic pain, mallutrition and nutrition, pancreatogenic diabetes, the natural course of the disease and quality of life [2].

It should be noted that all the recommendations, built on the basis of modern scientific data, are close to the framework. Following recommendations are given in the Russian consensus section on the diagnosis of the EPI:

1. In clinical practice, estimation of pancreatic elastase in feces should be used to identify exocrine pancreatic insufficiency, because this test is the most accessible.

2. After CP diagnosis, an examination of pancreas exocrine function should be conducted.

3. Progression or emergence of new symptoms that may be associated with EPI, are grounds for re-examination of its exocrine function, if previous data did not differ from the normal range.

4. Patients with diabetes mellitus have an increased risk of developing exocrine pancreatic insufficiency, therefore, if there are clinical signs, functional tests should be performed.

European recommendations, in response to the question "What analysis / research is indicated for the diagnosis of exocrine pancreatic insufficiency in clinical practice?", Indicate the following:

"In a clinical setting, it is necessary to conduct a non-invasive functional study of the pancreas. Fecal elastase-1 (FE-1) analysis is widely available, and a breath test using 13C-mixed triglycerides seems to be an alternative examination. The use of MRCP with secretin can also be used as a diagnostic method for exocrine pancreatic insufficiency, but this technique provides only "semi-quantitative data". Thus, estimation of pancreatic elastase in feces comes first concerning EPI diagnosis in everyday practice.

Approaches to the medical correction of exocrine pancreatic insufficiency are almost identical: the indications for replacement enzyme therapy are clinical symptoms or laboratory signs of malabsorption. To identify signs of mallutrition, it is recommended to conduct an appropriate nutritional assessment. The classic indication for enzyme replacement therapy is steatorrhea with the excretion of fat with feces at a level of> 15 g / day. However, the quantitative determination of fat in feces is often not carried out. Therefore, the indications for enzyme replacement therapy are also the pathological results of a functional study of the pancreas in conjunction with clinical signs of malabsorption or anthropometric and (or) biochemical signs of malnutrition. These signs include: weight loss, diarrhea, marked flatulence, and abdominal pain. Low values of the most common markers of nutritional deficiency (fat-soluble vitamins, prealbumin, retinol-binding protein and magnesium) are also an indication for the appointment of enzyme replacement therapy. Body weight, body mass

index, shoulder circumference, cholesterol, lymphocyte level, muscular strength of the hand (compression into a fist), symptoms of specific nutritional deficiency (hair loss, glossitis, dermatitis, parasthesia) can be used as other parameters of the clinical assessment of nutritional status.

The drugs of choice for the treatment of exocrine pancreatic insufficiency include microencapsulated pancreatine preparations in the enteric coating, the size is up to 2 mm. Micro- or mini-tablets of 2.2–2.5 mm in size can also be effective, although there is much less scientific evidence about this. Small differences are observed in relation to the recommended dose of lipase: according to the European recommendations, 40-50 thousand units with main meals should be used for initial therapy and half of this dose should be used for intermediate meals. Domestic recommendations offer 25 -40 thousand units for the main meal, and 10-20 thousand units for snacks with remark that we are talking about the minimum doses.

To assess the effectiveness of enzyme replacement therapy, it is proposed to determine the dynamics of symptoms associated with maldigestion (steatorrhea, weight loss, flatulence), and the parameters of the nutritional status of patients (anthropometric and biochemical). In the domestic recommendations, clinical indicators are suggested for evaluating effectiveness: weight gain, normalization of vitamin status, cessation of abdominal symptoms. The analysis of the data suggests that Russian and European approaches are identical in both diagnosis and treatment of exocrine pancreatic insufficiency in patients with CP.

However, a review of real practical recommendations given to patients with CP with exocrine pancreatic insufficiency in clinics or hospitals, doctors of various specialties (general practitioners, surgeons, less often - gastroenterologists) suggests that the above provisions on the required doses of multienzyme preparations are not always followed. Often you can find recommendations with an indication of the daily dose of the multienzyme medication 30 - 60 thousand units for lipase activity. There is an opinion among both patients and, unfortunately, individual doctors about the deterioration of the pancreas during the treatment with adequate (100-150 thousand units) doses of modern multienzyme medications. Another reason for non-compliance with the latest recommendations may be the high cost of microencapsulated pancreatin drugs.

The purpose of this study was to compare the effectiveness of enzyme replacement therapy with microencapsulated multienzyme preparations in patients with chronic pancreatitis with exocrine pancreatic insufficiency using adequate and low doses. The first group consisted of 40 patients with CP and exocrine pancreatic insufficiency, proved by the fecal elastase test results, and treated with enzyme replacement therapy at a dose of 100-150 thousand units for lipase activity, depending on the degree of exocrine pancreatic insufficiency. The second group consisted of 15 patients with CP with exocrine pancreatic insufficiency, who for various reasons (impossibility or reluctance, the existing recommendations of other doctors) received enzyme replacement therapy in a random dose, from 10 to 25 thousand units for lipase activity for food intake, the average dose amounted to 12.5 thousand units for a meal. The follow-up period was 3 months. General data is presented in table 1.

Table 1

Group	1 st	2 nd
Number of patients	40	15
Average age	54,9±13,8	54.7±14,0
Number of men	24 (60%)	9 (60%)
Number of women	16 (40%)	6 (40%)

Investigation of patients was the collection of complaints and anamnesis, physical examination, registration of anthropometric indicators (height, weight). Evaluation of clinical symptoms was carried out on a 5-point scale: 1 point - a symptom is absent, 2 points - symptom severity is weak (you cannot notice if you do not think), 3 points -

Table 2

Clinical and anamnestic data of patients of the studied groups

Group		1 st	2 nd
Number of patients		40	15
Duration of illness, years		4,1±7,2	2,9±3,9
Alcohol		24 (60%)	8 (53%)
Smoking		18 (45%)	7 (47%)
Complications of CP	Ectasia of Wirsung's duct	7 (17,5%)	8 (53%)
	Pancreatic Pseudocyst	11 (27,5%)	7 (47%)
	Lithiasis of Wirsung's duct	2 (5%)	2 (13%)
	Infiltrates	2 (5%)	2 (13%)
	Pancreas Fibrosis	7 (17,5%)	1 (7%)
	Pancreatic calcifications	5 (12,5%)	3 (20%)
Etiology of the disease	Alcoholic	25 (62,5%)	7 (47%)
	Biliary	5 (12,5%)	4 (27%)
	Idiopathic	8 (20%)	4 (27%)
	Pancreatectomy	2 (5%)	0 (0%)
Concomitant pathology	Duodenal ulcer	4 (10%)	0 (0%)
	Stomach ulcer	2 (5%)	0 (0%)
	Chronic alimentary hepatitis	6 (15%)	2 (13%)
	A history of cholecystectomy	7 (17,5%)	0 (0%)
	Cholelithiasis	2 (5%)	3 (20%)
	Chronic cholecystitis	1 (2,5%)	2 (13%)
	Diabetes	8 (20%)	3 (20%)

moderate symptom severity (you cannot ignore, but does not violate daily activity or sleep), 4 points - the severity of the symptom is strong (disrupts daytime activity or sleep), 5 points - the severity of the symptom is very strong (significantly disrupts daytime activity or sleep, rest is required); studied clinical and biochemical blood tests, conducted an ultrasound examination of the abdominal cavity organs. Determination of fecal elastase-1 was carried out by enzyme immunoassay (once at the beginning of the study). The results of the study with values above 200 μg / g of feces were considered normal, with values from 100 to 200 μg / g of feces, a moderate degree of exocrine pancreatic insufficiency was recorded, with values below 100 μg / g of feces - a pronounced degree of exocrine pancreatic insufficiency.

Statistical processing of the results was carried out using StatSoft STATISTICA 10 software. Student's t-test was used to analyze the parametric data, and Wilcoxon signed-rank test for non-parametric data. Differences with $p \leq 0.05$ were considered statistically significant.

Characteristics of the studied patients are presented in table 2.

Evaluation of parameters number of nutritional status is presented in table 3.

Table 3

Initial parameters of patients` nutritional status

Parameters	1 st group	2 nd group
BMI (kg / m^2)	22,2±3,5	20,4±2,8
Hemoglobin (g / l)	130,8±19,9	128,5±18,2
LYM	2,14±1,3	2,0±0,7
Cholesterol (mmol / l)	4,7±1,43	4,75±1,7
HDL (mmol / l)	1,25±0,36	1,2±0,5
Triglycerides (mmol / L)	1,34±0,73	1,4±0,6
Total protein (g / l)	70,5±8,9	63,6±16,4
Albumin (g / l)	36,1±6,7	29,8±10,3
Prothrombin index (%)	91,7±18,6	90,5±19,0

As demonstrated in the table, no significant differences in the studied parameters of the nutritional status were observed before treatment.

Comparison of clinical efficacy is presented in Tables 4 and 5.

The table shows that group 2 is characterized by a less pronounced dynamic in almost all symptoms.

Table 4

The frequency of symptoms before and after treatment

Parameters	1 st group		2 nd group	
	Before treatment	After treatment	Before treatment	After treatment
Pain	20 (50%)	12 (30%)	8 (53%)	5 (33%)
Heartburn	6 (15%)	0 (0%)	1 (7%)	1 (7%)
Nausea	4 (10%)	0 (0%)	1 (7%)	1 (7%)
Belching	2 (5%)	1 (2,5%)	10 (67%)	8 (53%)
Abdomen heaviness	22 (55%)	12 (30%)	3 (20%)	2 (13%)
Early satiety	19 (47,5%)	10 (25%)	4 (27%)	2 (13%)
Flatulence	29 (72,5%)	13 (32,5%)	5 (33%)	3 (20%)
Frequent bowel movements	20 (50%)	9 (22,5%)	0	0

Table 5

Symptom intensity before and after treatment

Parameters	1 st group		2 nd group	
	Before treatment	After treatment	Before treatment	After treatment
Pain	1,8±0,8	1,2±0,4*	1,73±0,8	1,3±0,5*
Heartburn	1,3±0,6	1*	1,1±0,3	1,1±0,3
Nausea	1,1±0,2	1	1,1±0,3	1,1±0,3
Belching	1,1±0,2	1,0±0,1	1,7±0,5	1,5±0,5
Abdomen heaviness	1,9±0,9	1,3±0,6*	1,26±0,6	1,15±0,4
Early satiety	1,7±0,8	1,3±0,4*	1,26±0,5	1,15±0,4
Flatulence	2,4±1,1	1,4±0,6*	1,33±0,5	1,23±0,4
Frequent bowel movements	2,1±1,2	1,3±0,6*	0,77±0,4	0,85±0,4

* differences are statistically reliable (t-test for paired samples, P≤0.05).

Table 6

Dynamics of clinical blood analysis

Indicator	1st group		2nd group	
	Before treatment	After treatment	Before treatment	After treatment
Erythrocytes (10^{12} / l)	4,4±0,7	4,5±0,7	4,2±0,5	3,9±0,6*
Hemoglobin (g / l)	130,85±21,7	135,0±14,9*	128,5±18,2	111,1±11,8
Platelets (10^9 / L)	275,9±115,1	253,8±72,2	301,6±77,5	441,5±280,4
Leukocytes (10^9 / l)	7,1±3,6	6,95±2,1	9,98±3,6	6,8±2,3*
Lymphocytes (%)	29,2±8,7	33,4±7,6*	21,2±11,8	22,3±16,8
LYM (10^9 / L)	2,14±1,3	2,6±1,1*	1,75±0,9	1,65±0,5
ESR (mm / hour)	12,4±7,5	11,0±6,1	15,2±7,6	26,8±12,9

* differences are statistically reliable (t-test for paired samples, P≤0.05).

Table 7

Dynamics of biochemical blood analysis

Indicator	1st group		2nd group	
	Before treatment	After treatment	Before treatment	After treatment
Cholesterol (mmol / l)	4,7±1,43	5,1±1,2*	4,75±1,7	4,8±1,6
HDL (mmol / l)	1,25±0,36	1,4±0,4*	1,2±0,5	1,1±0,5
Triglycerides (mmol / L)	1,34±0,73	1,47±0,7*	1,46±0,6	1,4±0,7
Total protein (g / l)	70,5±8,9	72,9±6,8*	63,6±16,4	65,1±7,7
Albumin (g / l)	36,1±6,7	40,9±5,8*	29,7±10,3	34,6±6,3
Prothrombin index (%)	91,7±18,6	97,4±15,4*	72,6±15,9	70,0±17,1

* differences are statistically reliable (t-test for paired samples, P≤0.05).

The intensity of the symptoms before and after treatment are presented in table 5

The table shows that in 1 group there was a significant positive dynamics of pain, heartburn, abdomen heaviness, early satiety, flatulence and bowel movements frequency, whereas group 2 showed a significant positive dynamic only of pain severity.

Comparison of laboratory studies presented in tables 6 and 7.

From the data presented in the table we can see that in group 1 there was a significant positive change in hemoglobin level, relative and absolute number of lymphocytes, whereas in group 2 there was a decrease in the level of erythrocytes and leukocytes, with an increase in ESR.

Dynamics of biochemical blood analysis is shown in Table 7.

Thus, in group 1, there was a significant positive trend in all the studied parameters, while in group 2, no reliable positive dynamics were found for any of them, moreover, there was a tendency to decrease in such parameters as total protein, albumin and prothrombin index.

Comparison of the dynamics of BMI. In the first group, there was a significant positive dynamics of BMI: from 22.2 ± 3.5 kg / m^2 to 23.0 ± 3.2 kg / m^2 (p = 0.000004), whereas in the second group there was no dynamics - from 20,4 ± 2,8 kg / m^2 to 20,2 ± 3,3 kg / m^2

Conclusion

The results of the study suggest that the use of multienzyme drugs for the treatment of exocrine pancreatic insufficiency in patients with chronic pancreatitis should be carried out in doses prescribed by modern guidelines. At the same time, there is significant positive dynamics of symptoms and improvement of anthropometric and biochemical markers of nutritional insufficiency. In case of treatment with insufficient doses, there is a positive dynamics of the clinical picture, however, there are no changes in the indicators characterizing the nutritional status, which indicates a low efficacy of therapy with insufficient doses of enzyme drugs. Despite the fact that the disappearance of clinical signs of malabsorption is generally considered the most important criterion for the success of enzyme replacement therapy, it has been shown that relief of symptoms is not always combined with normalization of nutritional status. A recent review showed that the best way to assess the effectiveness of enzyme replacement therapy is normalization of the nutritional status parameters, both anthropometric and biochemical [3].

Reference

1. Khatkov I.E., Mayev I.V., Bordin D.S. et al. Russian consensus on the diagnosis and treatment of chronic pancreatitis. Therapeutic archive / Terapevticheskiy arkhiv. 2017; 89(2): 105-113] DOI:10.17116/terarkh2017892105-113

2. J Matthias Lohr, E Dominguez-Munoz, J Rosendah et al. United European Gastroenterology evidence based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU) United European Gastroenterology Journal 2017; 5(2): 153–199

3.Lindkvist B, Phillips ME and Dominguez-Munoz JE. Clinical, anthropometric and laboratory nutritional markers of pancreatic exocrine insufficiency: Prevalence and diagnostic use. Pancreatology. 2015; 15:589–397.

Corresponding author
Minushkin Oleg
tantop@mail.ru

No conflict of interest stated.

Information about authors
O.N. Minushkin,
L.V. Maslovsky,
A.E. Evsikov,
A.M. Chebotareva

Doi 10.26269/jjd9-m989

Genetic roots of neuropsychiatric symptoms in Parkinson's disease

A.A. Ragimova, M.A. Samushiya
Central State Medical Academy of Department of Presidential Affairs, Moscow, Russia

Abstract

The literature review presents current data on the effect of the COMT, MAO-A, MAO-B, DAT, DRD2, VMAT2, TPH2 and SNCA genes on the course of Parkinson's disease, the effectiveness of therapy and their connection with a number of mental disorders. The work studies 77 articles and monographs devoted to the problems of genetics, neurology and psychiatry, published in the period from 1972 to 2018. Timely recognition of the genetic features of the course of the disease will optimize drug therapy, predict the development of early complications of the disease, such as cognitive decline, affective, obsessive-compulsive, psychotic disorders, as well as impulse-control disorders. Genetic prediction is also particularly relevant in the aspect of preparing and selecting patients for surgeries for deep brain stimulation.

Key words: Parkinson's disease, neurology, genetics, psychiatry.

Parkinson's disease is a neurodegenerative disease with a wide range of both motor and non-motor manifestations. The variability of the clinical picture due to various combinations of motor and non-motor symptoms is quite large, which requires finding new ways to optimally manage and predict the effectiveness of treatment, as well as determine the leading symptoms of disability.

Accumulation of new knowledge regarding neuropathology, neurochemistry and neuroimaging has led to consideration of the severity of the disease with a focus on "the overall severity of non-motor symptoms" [1,2] moving away from an isolated assessment of motor status [3].

It should be emphasized that in many cases the non-motor manifestations of a disease, in particular of neuropsychiatric rank, constitute a significant difficulty in managing patients, leading to neurochemical collisions when it is necessary to simultaneously correct affective, cognitive, motor and autonomic status. Based on this, the prediction of the development of neuropsychiatric symptoms in patients with PD is of great practical interest. One of these possibilities was the results of genetic studies of recent years, which revealed commonality of some changes in genome of psychiatric and neurodegenerative diseases. The resulting neurochemical cascades determine occurrence of mixed neuropsychiatric symptom complexes. The ability to study functioning of a gene in a continuous process during neurodegeneration and in conditions of exacerbation / remission of mental disorder provides a more holistic picture of the syndromes of neurotransmitter dysregulation as a single continuum, which despite the determining phenotypic differences between neurological and mental diseases, is determined by polygenetic factors.

Presumably, this equifinality effect is determined by both the direct influence of gene polymorphisms and the compensatory resources of the brain [3], which makes it possible to predict the variability and accentuation of the clinical picture of diseases with genetic intersections.

In particular, PD has been shown to develop dementia or mild cognitive impairment with a mutation in the glucocerebrosidase (GBA) gene, as well as the development of depression and sleep disorders during a mutation in the LRRK2 gene [5]. However, the most interesting are mutations, not only participating in the development of neuropsychiatric symptoms, but also changing the response to drug therapy (Table 1).

The evolution of views on the causes of the emergence of PD reflects the development of technology in the world and science [6]. The study of the genesis of PD became possible after appearance of methods of local toxic destruction of the black substance in primates, which formed basis of the theory of oxidative stress and influence of free radicals on the functioning of mitochondria. Traditionally, the most common targets for studying the genesis of PD are disorders of autophagy of nerve cells, as well as changes in the function of lysosomes and mitochondria, and a large number of researches have been devoted to the study of these aspects of PD appearance [7].

The development of genetics and the identification of the first PARK gene in 1977 shifted the emphasis in the study to the aspect of influencing the dynamics and clinical picture of PD genomic polymorphisms of -synuclein. The influence of the APPL2, NUCKS1, LAG3, SNCA Rep1 263, LRRK2 gene polymorphisms on the functioning of α-synuclein and the phenotypic features of mental and neurodegenerative diseases is

discussed in the world scientific literature. Identification of the genetic basis of familial cases of PD allowed identification of genetic predictors of the sporadic form of PD. Associated with hereditary forms of PD are the PARK1, PARK2, PARK5 genes, mutations of which cause disturbances in the ubiquintin-proteasome pathway of protein degradation, and PARK7, the mitochondrial nuclear protein gene, normally involved in the process of cell apoptosis [8-10].

The emergence of the possibility of sequencing individual DNA regions made it possible to introduce viral models for the occurrence of PD and intensively study the peculiarities of local expression of gene mutations that are involved in the occurrence of certain diseases, the dynamics of the spread of gene polymorphisms in the brain. The following areas of research into the genomic characteristics of PD seem to be relevant: the study of the features of the genes that determine the functioning of mitochondria and the effect of mutations in mitochondrial DNA on neuron activity and the release of neurotransmitters into the synaptic cleft; the effect of -synuclein variations on the functional state of the cell; the effect of gene mutations of lysosomal proteins on DNA repair, protein utilization, cell apoptosis; features of dopamine receptors, dopamine transfer proteins and proteins associated with dopamine cleavage [8-11].

The genetic method of learning is also used in psychiatry. The material of the meta-analysis of M. Nagel et al. (2018) presents promising areas for the study of the genesis of mental diseases: gene polymorphisms that influence the formation and functioning of dopaminergic, serotonergic neurons, GABAergic secondary projection spine neurons [12].

Due to the nosological diversity of mental diseases, it becomes possible to compare the genetic functioning of neurons during illness and remission on one group of cells, for example, when studying addiction disorders and recurrent depressive disorders, which is impossible due to irreversible changes in the spectrum model of neurodegenerative diseases.

The emergence of genetic research methods in a new way sanctifies the genesis of neurological and mental diseases, in which, despite the phenotypic differences, common polygenetic factors have been identified.

The study of the genome in psychiatry is characterized by a shift in attention to "positive" manifestations of mental disorders (psychosis, anxiety, depression, psychomotor agitation) [13-15] In neurology, however, there is a shift in emphasis on the loss or irreversible deterioration in the quality of a function (movement disorders, irreversible changes in personality structure, cognitive decline) [16].

The study of protective factors of both neurological and mental diseases seems promising. For example, the PARK16 locus responsible for DNA repair and timely utilization of non-functional proteins, including the genes rs823128 (NUCKS1), rs1572931 (RAB29), rs823156 (SLC41A1) is considered protective against PD [17], but not studied with respect to other diseases.

Another promising direction of studying the genetic features of mental and neurological diseases is the comparison of the genomic profile of diseases that reduce the likelihood of each other. In particular, the study of the SNAP25 genes SLC6A3, DAT1, DRD4, HTR1B, TPH2, SLC6A2, CDH13 did not show similar polymorphisms in patients with attention deficit disorder and PD, although both diseases are based on one or another pathology of the dopamine system homeostasis of the brain [18]. Despite the negative results, such information may shed light on the genesis of both psychiatric and neurological diseases. The comparison of the genetic and neurophysiological features of schizophrenia and PD seems to be promising. A sequential manifesto in one patient of these two diseases is a rare phenomenon and is an ambiguous task for a clinician [19]. In particular, it was shown on the model of application of typical antipsychotics, not only the effect on the D2 receptors of the brain, but also an increase in oxidative stress leads to the appearance of parkinsonism symptoms in psychiatric patients [20].

At first glance, schizophrenia and the spectrum of endogenous diseases and PD have a different genesis and different topical localization of the lesions of the long dopaminergic systems of the central nervous system: PD at the stage of motor symptoms will be characterized by predominant dysfunction of the nigrostriatal pathways of the mesostriatal system, while at schizophrenia there is a malfunction of mesolimbic and mesostriatal systems [21]. On the other hand, both diseases lead to deterioration of social functioning and a significant increase in economic costs, cognitive decline, narrowing the range of interests and simplifying cognitive activity, increasing dependence on others, in both diseases there can be deceptions of perception, delusions, affective and anxiety disorders [22].

Despite various violations of the cognitive sphere in the form of a violation of associative processes in schizophrenia and predominantly mental disorders against the background of increased rigidity of thinking in PD, there are a number of common cognitive characteristics (working, verbal memory, pace of performance, motor skills, speech fluency, planning) that undergo changes with the progression of both conditions [23,24], each of the diseases has its own most probable predictor genes: if for PD these are the genes responsible for supporting bruising genome integrity, protein utilization and timely apoptosis, dopaminergic neuroblasts, middle spine neurons, serotonergic neurons, vesicular leptomeningeal cells, radial glial cells, oligodendrocyte [12] progenitor are the most likely predictor genes for schizophrenia.

In the aspect of dopamine dysregulation, PD is comparable to the group of impulse-control disorders and a tendency to addictions. For example, a number of studies have shown an inverse correlation between smoking and PD [25]. The adherence to smoking also reflects the brain's ability to plasticize the release of dopamine in response to external influences, for example, stimulation with nicotine through an action on the acetylcholine system. The acetylcholine system is characterized by a variety of receptor subtypes (9 different types of α and β subunits), differing in localization and degree of permeability, and genetic features. The most sensitive to nicotine are α7-containing receptors located on the bodies and terminals of dopaminergic neurons in the ventral tegmental area and the compact part of the substantia nigra, which allows nicotine to directly influence and alter the impulse release of dopamine. The effect of nicotine is also noted on the prefrontal cortex, in which dopamine determines the executive function, motivation, plasticity of behavior and decision making for actions not only on the acetylcholine receptors, but on the glutamatergic and GABA system. Thus, the inverse correlation of PD and states of impulse-control disturbances or dependencies on surfactants is not only a statistically important indicator, but also shows new directions of approaches to treatment of PD and sheds light on aspects of PD genesis that were poorly understood before [26,27]

Materials and methods

In the review, 77 works were used, 75 of them were articles on genetics, clinical features of PD and mental diseases, 2 monographs on PD and psychiatry. 57 were published in the period from 2008 to 2018, 16 in the period from 1997 to 2007, 3 in the period from 1972 to 1995. 34 on the topic of the clinic and the genetic characteristics of PD.

42 articles were research papers (7,539 patients), as well as 7 studies on animal models and 2 studies performed in the laboratory by genome sequencing or creating a hybrid DNA model.

In neurological articles (13 papers), in addition to clinical observation, the most commonly used tests were UPDRS, QUIP score (Questionnaire for Impulsive Disorders in Parkinson's Disease-Rating Scale), MMSE (Mini-Mental State Examination), CES-D (Center for Epidemiologic Studies Depression Scale).

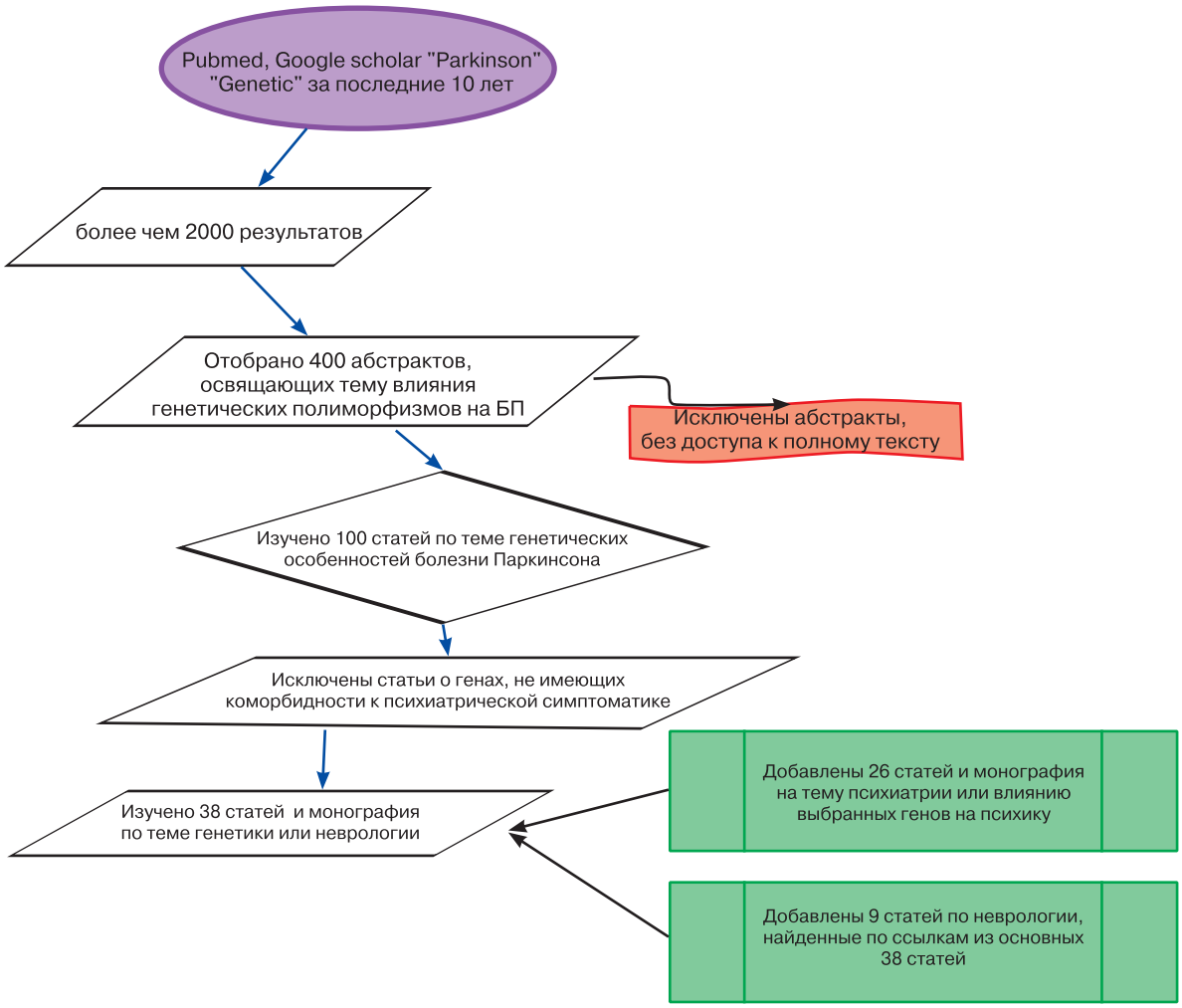


Рисунок. Схема отбора литературы.

Psychiatric articles (29 papers) noted the use of WAIS-R tests (Silverstein's method with scores from the Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale-Revised), SCID-IV (Structured Clinical Interview for DSM-IV), ToM (test used to evaluate social cognition), Thematic Apperception Test , PANSS, CBCL/6–18 (Child Behavior Checklist for the age range of 6–18 years old), HAM-D (Hamilton Depression Rating Scale), CDSS (Calgary depression scale for schizophrenia), MINI (Mini International Neuropsychiatric Interview) , HAMD-17 (Hamilton Rating Scale for Depression), HAMA (Hamilton Anxiety Scale).

The study used 43 literature reviews, 7 - meta-analyzes: 3 reviews on genetics, 7 reviews and 2 meta-analyzes on psychiatry, 16 reviews and 5 meta-analyzes on the topic of PD.

Further, the review examined current studies highlighting some of the genetic features of Parkinson's disease (PD) and the genetic relationship between PD and a number of mental illnesses.

1. COMT - Catechol-O-methyltransferase catalyzes the breakdown of catecholamines: dopamine, epinephrine, norepinephrine. COMT polymorphisms in the cortico-striatal pathways of the brain are involved in the formation of early dementia in PD, regardless of the progression of motor disorders [28]. Antipsychotic medication was present in 30% of patients with a view to curing mental symptoms years before the onset of motor manifestations of PD, which subsequently delayed the verification of PD by expanding the scope of diagnostic search [29].

The appearance of mental disorders long before the manifestation of the first motor symptoms of PD is consecrated within the framework of two theories. On the one hand, the concept of H. Braak ("Braakhypothesis" 2003) presents mental disorders in the premorbid period as a manifestation of the first two stages of PD formation, during which the serotonergic nuclei of the brain stem seam is affected long before the substance is damaged. According to another point of view, affective pathology in the premorbid period of PD is caused by the pathology of a neurobiological substrate common to both mental and neurological diseases [30].

In addition to PD, the 22q11.2 deletion syndrome (COMT gene) was studied on a model of mental illness: 24% of carriers of COMT polymorphism show symptoms of a psychotic register in a history, 31.4% have affective and anxiety disorders. [31,32]. The effect of the deletion of the COMT gene is also noted in patients with schizophrenia, in whom the 22q11.2 locus polymorphism occurs in 1% of cases and determines the phenotype of patients. Patients with schizophrenia who carry a 22q11.2 deletion phenotypically differ in the early onset of the disease from 12 to 26 years, a lesser severity of negative disorders, a tendency to explosive reactions and impulsive actions [33]. The 22q11.2 deletion carriers are also distinguished by the features of cognitive function: 40% had moderate mental retardation, poor results in tests for motor skills, verbal skills and social intelligence [34].

Thus, common to carriers of COMT gene polymorphisms, both PD patients and psychiatric patients, will have symptoms of early cognitive decline, a history of mental illness and subsequent antipsychotic or dopaminergic therapy, which reflects a metabolic catecholamine caused by the genetic characteristics of the COMT enzyme.

2. MAO - (monoamine oxidase), an enzyme that participates in the catabolism of both endogenous and exogenous monoamines and is encoded by an X-linked gene, which causes uneven phenotypic manifestations of MAO depending on the sex of the patient [11,12]. MAO is divided into two subspecies: MAO A is a fermenting adrenaline, noradrenaline, serotonin, histamine, dopamine, and highly specialized MAO-B, the substrates for which are phenylethylamine and dopamine. MAO-B polymorphisms, which slow down or accelerate the function of monoamine oxidase, cause dyskinesia at the peak of the levodopa dose, accelerate cognitive decline. [35].

The participation of the rs1137070 and rs3741049 polymorphisms (A / A allele) of the MAO enzyme was noted in the formation of depressive disorders, including those that are not sensitive to placebo [36,37], bipolar affective disorders [38], schizophrenia [39], and borderline personality disorder [40], and the formation of attention deficit disorder in adolescents [41,42]. Genetic variations of MAO, together with SERT, and to a lesser extent COMT, determined the phenotypic features of depressive patients with schizophrenia in the form of aggression, impulsivity, speedy increase of negative symptoms.

Common to PD and mental disorders in the disruption of the functioning of MAO are a rapid decline in cognitive function, the paradox of the action of drugs (dopaminergic drugs, antidepressants) [43], as well as a predisposition to occurrence of affective disorders throughout life.

3. DRD1, DRD2, DRD3 - dopamine receptor genes. Polymorphism of the gene encoding D2 receptors (rs1800497) is associated with a decrease in the density of dopamine receptors in the striatum, which leads to the formation of parkinsonian symptoms [44]. DRD2 (rs1800497) and DRD1 (rs4532 and rs4867798) polymorphism carriers, despite being well tolerated by dopamine replacement therapy, are at risk of impulse control disorders, due to the effect of dopaminergic therapy on the ventral striatum, the most associated with the symptoms of the pathological search for positive reinforcement [45.46].

Studies in the general population showed the involvement of DRD2 mutations in the formation of behavioral control disorders and addictive disorders: according to O.H. Della Torre (2018) DRD2 polymorphism (rs6277) determines the personality characteristics of children: a tendency to conflict and ignoring social norms. A decrease in the density of DRD2 / 3 receptors in the striatum is observed among adults with impaired learning function (dependence on positive reinforcement) [47,48].

4. DAT is a transmembrane transporter of dopamine, which reverses it from the synaptic cleft into the cytosol of the cell and it is associated with a large number of neuropsychiatric disorders. Recessive polymorphism of the DAT gene with a variant number of tandem repeats (DAT1-VNTR) of the 3'-region is often found in PD [49].

Polymorphisms DAT1-VNTR, rs27072, rs27048 and rs2963238 were found in 24% of patients with alcoholism in a study on the European population, they lead to more severe alcoholic palimpsests and the formation of dependence, in particular to methylphenidate, the DAT blocker, which has a psycho-stimulating effect. [50, 51]. The DAT gene together with the COMT genes, dopamine (DRD1, DRD2, DRD3, DRD4) and serotonin receptors, serotonin transporters (HTR2A, 5HTT), and glutamate receptors (GRIN2B), is involved in the formation of obsessive-compulsive behavior in PD [52]

5. 5TPH2 (tryptophan hydroxylase) - an enzyme involved in the synthesis of serotonin and melatonin, together with VMAT2 determine the functioning of the serotonin system in PD, while the relationship between the serotonin transporter SERT and PD was refuted in L. Gao meta-analysis (2014), created on the basis of 9 studies of the genetic characteristics of PD and the association of PD with depression. Tryptophan hydroxylase participates in the first stage of serotonin synthesis, catalyzes the addition of the –HO group (hydroxylation) to 5-hydroxytryptophan, affects the transcription of serotonin receptor RNA (5HT) and is predominantly (up to 50%) localized in the striatum and prefrontal cortex [53,54]. Normally, the activity of 5HT receptors inhibits the action of dopamine in the ventral part of the tire and the accessory brain nucleus [55], while the level of serotonin decreases, a decrease in the tonic inhibitory effect on dopamine and impaired fronto-striatal pathways is observed, which is reflected in impulsive behavior and a decrease in criticism to errors and increased search behavior [56,57].

The study of TPH2 mutations in PD is most relevant in terms of impulsive behavior and abuse of dopaminergic drugs. TPH2 mutations (rs1352250, rs6582078 SNPs, GGA haplotype) determined the severity of additive behavior in PD, which is not corrected with a decrease in the dosage of drugs [58].

Interconnection TPH2 and impulsive behavior also proved to psychiatric samples: polymorphisms rs6582078 and rs1352250 predisposed to risky behavior and acceptance of impulsive solutions [59], affective carriers of rs7305115 A / G and G / G alleles are at risk of suicide attempt [60].

6. SNCA - the gene encoding alpha-synuclein, presynaptic chaperone, is the dominant gene and is found in familial forms of PD with dominant inheritance. The repeated SNCA polymorphism is called REP1; in the presence of a long SNCA Rep1 263 allele, the risk of developing PD increases: the risk of oxidative stress increases. Reduced SNCA transcription, although a protective factor for PD, increases the risk of alcohol abuse, which in turn increases the likelihood of polymorphisms [61].

Although the study of SNCA pathology is associated with the motor sphere, it is important to pay attention to the non-motor aspects of PD: SNCA carriers (Rep1 263) were distinguished by a quick early onset of the disease, an increase in dementia and the presence of hallucinations that occurred and develop independently of the dynamics of the motor symptoms. [62].

7. VMAT2 is an integral membrane protein that transports and packs monoamines: dopamine, norepinephrine, serotonin and histamine, from the cell cytosol to synaptic vesicles, and is involved in the breakdown of toxic cytosolic unpackaged dopamine, which becomes vulnerable to creating active oxygen forms [63]. In the nigrostriatal and mesolimbic pathways, VMAT2 is involved in the vesicular release of GABA. On the basis of the amplified DNA of two African and European ethnic groups, polymorphisms were detected, these groups increase the synthesis of VMAT2 (rs60543597, rs12412905), which is a protective factor for PD [64]. S.P. Alter study (2016), conducted in mice, showed that a decrease in the expression of the VMAT2 gene (SLC18A2) does not affect the degradation of serotonergic cells, but increases the sensitivity of 5-HT1A autoreceptors, most common in the human CNS [65,66]. A partial decrease in VMAT2 production ("VMAT2 knockout") negatively affects the elimination of endogenous neurotoxins and stimulates the development of oxidative stress, an important stage in the pathogenesis of PD [67; 68]. The decrease in VMAT2 production was correlated with the appearance of non-depressive apathy, with PD on a mouse brain model in the form of reducing the need for home improvement and reducing interest in sugar, while maintaining the results of the swimming test within the norm, which indicates the absence of an affective component in the behavior. [69]. VMAT2 gene mutations are found in most narcological, psychiatric and neurological diseases, as well as being one of the nine defining gene markers for schizophrenia (CHGB, SLC18A2, SLC25A27, ESD, C4A / C4B, TCP1, CHL1, CTNNA2) [70].

8. GABA (GABA) - γ-Aminobutyric acid inhibitory neurotransmitter central nervous. GABA has an inhibitory effect on the release of dopamine and noradrenaline in the frontal lobes, while the activity of the GABA neurons themselves is under the control of serotonin: activation of 5-HT2C receptors leads to an increase in GABA activity and a decrease in dopamine in the frontal lobes. This mechanism probably explains both the appearance of apathy with long-term therapy with antidepressants from the SSRI group, and the anti-apathetic action of 5-HT2C inhibitors (Fluoxetini, Agomelatini) [71,72].

According to https://www.snpedia.com, a resource reporting information about polymorphisms in the human genome, in humans, the GABA function is encoded in 29 genes on different chromosomes, with many variants of polymorphisms that encode for synthesis, degradation, transport, and GABA receptors.

he involvement of GABA in the pathogenesis of PD is traced at all stages of the formation of the dis-

Table

Variants of gene mutations that affect the therapy and phenotypic features of Parkinson's disease are promising for study in clinical practice

Substrate	Polymorphism	Chromosome	Phenotypic features	Clinical manifestation	Tests	The number of patients examined	Author
COMT	rs6269 rs4633 rs4818 rs4680	22	Change COMT activity	The rapid increase of cognitive defect	MMSE	409	Lin C.H., 2018
COMT	COMT H/H	22	High COMT activity	The need for high doses of levodopa	-	162	Sampaio T.F., 2018
COMT	COMT L/L	22	Low COMT activity	The need for high doses of levodopa	-	162	Sampaio T.F., 2018
COMT	22q11.2 делеция	22	Change COMT activity	The presence of mental disorders before the manifestation of PD, the high prevalence of mental non-motor disorders against the background of the reception Levodopa	-	Systematic review of 45 clinical cases	Boot E., 2015
MAO-B	MAO-B A/A	X-chromosome	MAO-B activity decrease	The emergence of dyskinesia on the background of the peak dose of Levodopa	-	95 patients	Białecka M., 2004
MAO-B	MAO-B G/G	X-chromosome	Increased MAO-B activity	The need for high doses of levodopa	-	95 patients	Białecka M., 2004
DAT	rs3836790 rs28363170	5	Increase in the main concentration of dopamine transporter	Best effect L -DOPA on motor functions (gait) UPDRS	UPDRS	61 patients	Moreau C., 2015
DRD2	rs1800497 (Taq1 Apolymorphism A1 / A1 A1 / A2)	11	Decreased baseline dopamine in the striatum	Increased risk of impulse-control disorders inpatients with a dopaminergic therapy	UPDRS CES-D MMSE QUIP	11 пациентов	McDonel K.E., 2018
VMAT2	rs60543597, rs12412905	10	Increase VMAT2 output	Reducing the risk of PD	-	Amplified DNA of African and European samples	Glatt C.E., 2006
TPH2	rs1352250, rs6582078, GGA haplotype	12	Reduced TPH2 production	Increased risk of impulse control disorders	Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale QUIP MMSE 154 patient	154 patients	Gao L., 2014
SNCA	SNCA (Rep1 263)	4	Enhancement of SNCA expression	Increased risk of early onset of PD, complicated by psychotic events and an increase in dementia	-	426 patients	Corrado L., 2018

ease. In the early stages of the disease, the pathology of GABA affects functioning of posterior nuclei of the vagus nerve, nucleus of the glossopharyngeal nerve, locus coeruleus, hypothalamus, mesolimbic and nigrostriatal dopaminergic systems, which clinically manifested in violations of the gastrointestinal tract, loss or change in sense of smell, sleep disorders and the emergence of anxiety, anhedonia, apathy, hypomimia and difficulty in motivating movement [73,74]. At the stages of the first motor symptoms of GABA disease, there is an imbalance of GABA in the central nervous system: an increase in GABA in the striatopallidal complex promotes the development of bradykinesia and rigidity, reduces tremor and postural instability. During the collapse of the GABA system, there is a decrease in cognitive and motor function due to the effect on the striato-hippocampal and thalamocortical system [75].

At the moment, there is a certain lack of information on the effect of mutations of GABA genes on mental and neurodegenerative diseases.

9. PINK1 is a recessive gene that affects the functioning of the Parkin gene, the activity of which determines the timely autophagy of depolarized mitochondria. In the clinical case, L. Ephraty et al., (2007) of a familial PD disease in PINK1 mutation carriers were brothers 25 and 33 years old, they had an early manifestation of the disease in the form of anxiety-depressive disorder with antisocial behavior and impulse-control disorders. The parents of the patients had behavioral disorders and a tendency to affective diseases without signs of parkinsonism [76].

Prospects for the study of genetic features, comorbid mental pathology, with PD in clinical practice.

Evaluation of genetic features in order to determine a patient's treatment strategy is a common practice worldwide [77]. The study of such enzymes as COMT, MAO-A, MAO-B, DAT, DRD2, VMAT2, TPH2 and SNCA is a promising direction for personalized treatment of PD.

An important aspect of the study of genetic features in clinical practice is the determination of the prospects for the operation of deep brain stimulation (DBS). In a study by E. Lohmann et al. (2008) patients of PD were treated with Parkin gene carriers in comparison with the sporadic form of PD and the heterozygous form of PD [78]. The Parkin gene encodes ubiquitin ligase, which regulates mitochondrial DNA recovery, mitochondrial division, timely elimination of non-functional proteins, is characterized by recessive inheritance, i.e. for complete phenotypic manifestation, two mutations in the carrier DNA are necessary. Parkin mutation carriers are characterized by early onset of the disease, slow progression and good response to dopaminergic therapy drugs [79] 24 months after surgery, homozygous Parkin carriers were characterized by lower doses of dopaminergic therapy, but they had worse results on testing the cognitive decline on the MATTIS scale.

Thus, the assessment of genetic features in order to determine a patient's treatment strategy is a common practice throughout the world [77, 80]. The study of such enzyme genes as COMT, MAO-A, MAO-B, DAT, DRD2, VMAT2, TPH2 and SNCA is a promising direction in developing personalized therapy strategies based not only on the assessment of clinical status, but also on their endophenotype, as well as reflects the transition from the nosological approach to the study of both mental and neurological disorders to the dimensional one.

Reference

1. *Todorova A, Jenner P, Ray Chaudhuri K. Non-motor Parkinson's: integral to motor Parkinson's, yet often neglected. Practical Neurol. 2014; 14(5): 310-322. doi:10.1136/practneurol-2013-000741*
2. *Barone, P. et al. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Movement Disorders. 2009; 24(11): 1641-1649. doi:10.1002/mds.22643*
3. *Hoehn M, Yahr M. Parkinsonism: onset, progression and mortality. Neurology. 1967; 17(5): 427–42. doi:10.1212/wnl.17.5.427. PMID 6067254.*
4. *Snezhnevsky A.V. Schizophrenia. Multidisciplinary research. Medicine; 1972.*
5. *Katunina E, Titova N. The epidemiology of nonmotor symptoms in PD (cohort and other studies). In: Chaudhuri KR, Titova N, editors. Nonmotor Parkinson's: The Hidden Face. International Review of Neurobiology. Vol. 33. Cambridge, MA: Academic Press is an imprint of Elsevier; 2017. ISSN 0074-7742. http://dx.doi.org/10.1016/bs.irn.2017.05.012. 13.*
6. *Gelders G, Baekelandt V, Perren, AV. Linking Neuroinflammation and Neurodegeneration in Parkinson's Disease. Journal of Immunology Research.2018; 1-12. doi:10.1155/2018/4784268*
7. *Chang D, Nalls MA, Hallgrímsdóttir IB, Hunkapiller J, Van der Brug M, Cai F, et al. A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. NatureGenetics. 2017; 49(10): 1511-16. doi:10.1038/ng.3955*
8. *George G, Singh S, Lokappa SB, Varkey J. Gene co-expression network analysis for identifying genetic markers in Parkinson's disease - a three-way comparative approach. Genomics. 2018. doi:10.1016/j.ygeno.2018.05.005*
9. *Freeze B, Acosta D, Pandya S, Zhao Y, Raj A. Regional expression of genes mediating trans-synaptic alpha-synuclein transfer predicts regional atrophy in Parkinson disease. NeuroImage: Clinical. 2018;18:456-466. doi:10.1016/j.nicl.2018.01.009.*
10. *Corrado L, Marchi FD, Tunesi S, Oggioni GD, Carecchio M, Magistrelli L. et al. The Length of SNCA Rep1 Microsatellite May Influence Cognitive Evolution in Parkinson's Disease. Frontiers in Neurology. 2018;9. doi:10.3389/fneur.2018.00213.*
11. *Wooten GF. Are men at greater risk for Parkinsons disease than women? Journal of Neurology, Neurosurgery & Psychiatry. 2004;75(4):637-639. doi:10.1136/jnnp.2003.020982.*
12. *Nagel M, Jansen PR, Stringer S, et al. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. Nature Genetics. 2018;50(7):920-927. doi:10.1038/s41588-018-0151-7.*
13. *St Clair, D. (2009). Copy Number Variation and Schizophrenia. SchizophreniaBulletin, 35(1), 9-12. doi:10.1093/schbul/sbn147*

14. Jr EHC, Scherer SW. Copy-number variations associated with neuropsychiatric conditions. Nature. 2008;455(7215):919-923. doi:10.1038/nature07458.

15. Adams DH, Close S, Farmen M, Downing AM, Breier A, Houston JP. Dopamine receptor D3 genotype association with greater acute positive symptom remission with olanzapine therapy in predominately caucasian patients with chronic schizophrenia or schizoaffective disorder. Human Psychopharmacology: Clinical and Experimental. 2008;23(4):267-274. doi:10.1002/hup.930.

16. Domingo A, Klein C. Genetics of Parkinson disease. Neurogenetics, Part I Handbook of Clinical Neurology. 2018:211-227. doi:10.1016/b978-0-444-63233-3.00014-2.

17. Bai Y, Dong L, Huang X, Zheng S, Qiu P, Lan F. Associations of rs823128, rs1572931, and rs823156 polymorphisms with reduced Parkinson's disease risks. NeuroReport. 2017;28(14):936-941. doi:10.1097/wnr.0000000000000846.

18. Geissler JM, Romanos M, Gerlach M, Berg D, Schulte C. No genetic association between attention-deficit/hyperactivity disorder (ADHD) and Parkinson's disease in nine ADHD candidate SNPs. ADHD Attention Deficit and Hyperactivity Disorders. 2017;9(2):121-127. doi:10.1007/s12402-017-0219-8.

19. Gadit A. Schizophrenia and Parkinsons disease: challenges in management. Case Reports. 2011;2011(dec17 1). doi:10.1136/bcr.11.2011.5108.

20. Ghanemi A. Schizophrenia and Parkinson's disease: Selected therapeutic advances beyond the dopaminergic etiologies. Alexandria Journal of Medicine. 2013;49(4):287-291. doi:10.1016/j.ajme.2013.03.005.

21. Birtwistle J, Baldwin D. Role of dopamine in schizophrenia and Parkinsons disease. British Journal of Nursing. 1998;7(14):832-841. doi:10.12968/bjon.1998.7.14.5636.

22. Aro S, Aro H, Keskimäki I. Socio-economic Mobility among Patients with Schizophrenia or Major Affective Disorder a 17-Year Retrospective Follow-Up. British Journal of Psychiatry. 1995;166(06):759-767. doi:10.1192/bjp.166.6.759.

23. Petrova N.N., Dorofeikova M.V., Voinkova E.E. Cognitive disorders in patients with schizophrenia at different stages of the disease. Zhurnal nevrologii i psikhiatrii im SS Korsakova. 2016;116(4):10. doi:10.17116/jnevro20161164110-15.

24. Levin O.S., Fedorova N.V. Parkinson's disease. M: Medpressinform; 2012

25. Ritsner MS. Brain Protection in Schizophrenia, Mood and Cognitive Disorders. Dordrecht: Springer; 2010. ISBN 978-90-481-8553-5

26. Livingstone PD, Wonnacott S. Nicotinic acetylcholine receptors and the ascending dopamine pathways. Biochemical Pharmacology. 2009;78(7):744-755. doi:10.1016/j.bcp.2009.06.004.

27. Quik M, Oleary K, Tanner CM. Nicotine and Parkinsons disease: Implications for therapy. Movement Disorders. 2008;23(12):1641-1652. doi:10.1002/mds.21900.

28. Lin C-H, Fan J-Y, Lin H-I, Chang C-W, Wu Y-R. Catechol-O-methyltransferase (COMT) genetic variants are associated with cognitive decline in patients with Parkinsons disease. Parkinsonism & Related Disorders. 2018;50:48-53. doi:10.1016/j.parkreldis.2018.02.015.

29. Boot E, Butcher NJ, Udow S, et al. Typical features of Parkinson disease and diagnostic challenges with microdeletion 22q11.2. Neurology. 2018;90(23). doi:10.1212/wnl.0000000000005660.

30. Wang S, Mao S, Xiang D, Fang C. Association between depression and the subsequent risk of Parkinsons disease: A meta-analysis. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018;86:186-192. doi:10.1016/j.pnpbp.2018.05.025.

31. Fung WLA, Mcevilly R, Fong J, Silversides C, Chow E, Bassett A. Elevated Prevalence of Generalized Anxiety Disorder in Adults With 22q11.2 Deletion Syndrome. American Journal of Psychiatry. 2010;167(8):998-998. doi:10.1176/appi.ajp.2010.09101463.

32. Wither RG, Borlot F, Macdonald A, et al. 22q11.2 deletion syndrome lowers seizure threshold in adult patients without epilepsy. Epilepsia. 2017;58(6):1095-1101. doi:10.1111/epi.13748.

33. Bassett AS, Chow EW. Schizophrenia and 22q11.2 deletion syndrome. Current Psychiatry Reports. 2008;10(2):148-157. doi:10.1007/s11920-008-0026-1.

34. Chow EW, Watson M, Young DA, Bassett AS. Neurocognitive profile in 22q11 deletion syndrome and schizophrenia. Schizophrenia Research. 2006;87(1-3):270-278. doi:10.1016/j.schres.2006.04.007.

35. Bialecka M, Drozdzik M, Klodowska-Duda G, et al. The effect of monoamine oxidase B (MAOB) and catechol-O-methyltransferase (COMT) polymorphisms on levodopa therapy in patients with sporadic Parkinsons disease. Acta Neurologica Scandinavica. 2004;110(4):260-266. doi:10.1111/j.1600-0404.2004.00315.x.

36. Zhang J, Chen Y, Zhang K, et al. A cis-Phase Interaction Study of Genetic Variants Within the MAOA Gene in Major Depressive Disorder. Biological Psychiatry. 2010;68(9):795-800. doi:10.1016/j.biopsych.2010.06.004.

37. Leuchter AF, Mccracken JT, Hunter AM, Cook IA, Alpert JE. Monoamine Oxidase A and Catechol-O-Methyltransferase Functional Polymorphisms and the Placebo Response in Major Depressive Disorder. Journal of Clinical Psychopharmacology. 2009;29(4):372-377. doi:10.1097/jcp.0b013e3181ac4aaf.

38. Lin Y-MJ, Davamani F, Yang W-C, Lai T-J, Sun HS. Association analysis of monoamine oxidase A gene and bipolar affective disorder in Han Chinese. Behavioral and Brain Functions. 2008;4(1):21. doi:10.1186/1744-9081-4-21.

39. Wei Y-L, Li C-X, Li S-B, Liu Y, Hu L. Association study of monoamine oxidase A/B genes and schizophrenia in Han Chinese. Behavioral and Brain Functions. 2011;7(1):42. doi:10.1186/1744-9081-7-42.

40. Ni X, Sicard T, Bulgin N, et al. Monoamine oxidase A gene is associated with borderline personality disorder. Psychiatric Genetics. 2007;17(3):153-157. doi:10.1097/ypg.0b013e328016831c.

41. Huang S, Cook DG, Hinks LJ, et al. CYP2A6, MAOA, DBH, DRD4, and 5HT2A genotypes, smoking behaviour and cotinine levels in 1518 UK adolescents. Pharmacogenetics and Genomics. 2005;15(12):839-850. doi:10.1097/01213011-200512000-00002.

42. Li J, Kang C, Zhang H, et al. Monoamine oxidase A gene polymorphism predicts adolescent outcome of attention-deficit/hyperactivity disorder. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2007;144B(4):430-433. doi:10.1002/ajmg.b.30421.

43. Aboukarr A, Giudice M. Interaction between Monoamine Oxidase B Inhibitors and Selective Serotonin Reuptake Inhibitors. The Canadian Journal of Hospital Pharmacy. 2018;71(3). doi:10.4212/cjhp.v71i3.2586.

44. Mcdonell KE, Wouwe NCV, Harrison MB, Wylie SA, Claassen DO. Taq1A polymorphism and medication effects on inhibitory action control in Parkinson disease. Brain and Behavior. 2018;8(7). doi:10.1002/brb3.1008.

45. Heiden P, Heinz A, Romanczuk-Seiferth N. Pathological gambling in Parkinsons disease: what are the risk factors and what is the role of impulsivity? European Journal of Neuroscience. 2016;45(1):67-72. doi:10.1111/ejn.13396.

46. Abidin SZ, Tan EL, Chan S-C, Jaafar A, Lee AX, Abd Hamid MH. et al. DRD and GRIN2B polymorphisms and their association with the development of impulse control behaviour among Malaysian Parkinson's disease patients. BMC Neurology. 2015;15(1). doi:10.1186/s12883-015-0316-2.

47. Torre OHD, Paes LA, Henriques TB, ., De Mello MP, Celeri EH, Dalgalarrondo P. et al. Dopamine D2 receptor gene polymorphisms and externalizing behaviors in children and adolescents. BMC Medical Genetics. 2018;19(1). doi:10.1186/s12881-018-0586-9.

48. Dang LC, Samanez-Larkin GR, Castrellon JJ, Perkins SF, Cowan RL, Zald DH. Individual differences in dopamine D2 receptor availability correlate with reward valuation. Cognitive, Affective, & Be-

havioral Neuroscience. 2018;18(4):739-747. doi:10.3758/s13415-018-0601-9.

49. Aversa D, Martini A, Guatteo E, Pisani A, Mercuri NB, Berretta N. Reversal of dopamine-mediated firing inhibition through activation of the dopamine transporter in substantia nigra pars compacta neurons. British Journal of Pharmacology. 2018;175(17):3534-3547. doi:10.1111/bph.14422.

50. Moreau C, Meguig S, Corvol J-C, Labreuche J, Vasseur F, Duhamel A. et al. Polymorphism of the dopamine transporter type 1 gene modifies the treatment response in Parkinson's disease. Brain. 2015;138(5):1271-1283. doi:10.1093/brain/awv063.

51. Strat YL, Ramoz N, Pickering P, et al. The 3 Part of the Dopamine Transporter Gene DAT1/SLC6A3 Is Associated With Withdrawal Seizures in Patients With Alcohol Dependence. Alcoholism: Clinical and Experimental Research. 2007;32(1):27-35. doi:10.1111/j.1530-0277.2007.00552.x.

52. Cormier F, Muellner J, Corvol J-C. Genetics of impulse control disorders in Parkinson's disease. Journal of Neural Transmission. 2012;120(4):665-671. doi:10.1007/s00702-012-0934-4.

53. Gao L, Gao H. Association between 5-HTTLPR polymorphism and Parkinson's disease: a meta analysis. Molecular Biology Reports. 2014;41(9):6071-6082. doi:10.1007/s11033-014-3484-z.

54. Cilia R, Benfante R, Asselta R, Marabini L, Cereda E, Siri C, et al. Tryptophan hydroxylase type 2 variants modulate severity and outcome of addictive behaviors in Parkinsons disease. Parkinsonism & Related Disorders. 2016;29:96-103. doi:10.1016/j.parkreldis.2016.05.017.

55. Daw ND, Kakade S, Dayan P. Opponent interactions between serotonin and dopamine. Neural Networks. 2002;15(4-6):603-616. doi:10.1016/s0893-6080(02)00052-7.

56. Nakamura K, Matsumoto M, Hikosaka O. Reward-Dependent Modulation of Neuronal Activity in the Primate Dorsal Raphe Nucleus. Journal of Neuroscience. 2008;28(20):5331-5343. doi:10.1523/jneurosci.0021-08.2008.

57. Rogers RD. The Roles of Dopamine and Serotonin in Decision Making: Evidence from Pharmacological Experiments in Humans. Neuropsychopharmacology. 2010;36(1):114-132. doi:10.1038/npp.2010.165.

58. Cilia R, Benfante R, Asselta R, Marabini L, Cereda E, Siri C. et al. Tryptophan hydroxylase type 2 variants modulate severity and outcome of addictive behaviors in Parkinsons disease. Parkinsonism & Related Disorders. 2016;29:96-103. doi:10.1016/j.parkreldis.2016.05.017.

59. Juhasz G, Downey D, Hinvest N, Thomas E, Chase D, Toth ZG. et al. Risk-Taking Behavior in a Gambling Task Associated with Variations in the Tryptophan Hydroxylase 2 Gene: Relevance to Psychiatric Disorders. Neuropsychopharmacology. 2009;35(5):1109-1119. doi:10.1038/npp.2009.216.

60. Ke L, Qi ZY, Ping Y, Ren CY. Effect of SNP at position 40237 in exon 7 of the TPH2 gene on susceptibility to suicide. Brain Research. 2006;1122(1):24-26. doi:10.1016/j.brainres.2006.09.007.

61. Levey DF, Le-Niculescu H, Frank J, et al. Genetic risk prediction and neurobiological understanding of alcoholism. Translational Psychiatry. 2014;4(5). doi:10.1038/tp.2014.29.

62. Corrado L, Marchi FD, Tunesi S, et al. The Length of SNCA Rep1 Microsatellite May Influence Cognitive Evolution in Parkinson's Disease. Frontiers in Neurology. 2018;9. doi:10.3389/fneur.2018.00213.

63. Lohr KM, Miller GW. VMAT2 and Parkinson's disease: harnessing the dopamine vesicle. Expert Review of Neurotherapeutics. 2014;14(10):1115-1117. doi:10.1586/14737175.2014.960399.

64. Glatt CE, Wahner AD, White DJ, Ruiz-Linares A, Ritz B. Gain-of-function haplotypes in the vesicular monoamine transporter promoter are protective for Parkinson disease in women. Human Molecular Genetics. 2005;15(2):299-305. doi:10.1093/hmg/ddi445.

65. Alter SP, Stout KA, Lohr KM, Taylor TN, Shepherd KR, Wang M. et al. Reduced vesicular monoamine transport disrupts serotonin signaling but does not cause serotonergic degeneration. Experimental Neurology. 2016;275:17-24. doi:10.1016/j.expneurol.2015.09.016.

66. Gilliam T, Freimer NB, Kaufmann CA, et al. Deletion mapping of DNA markers to a region of chromosome 5 that cosegregates with schizophrenia. Genomics. 1989;5(4):940-944. doi:10.1016/0888-7543(89)90138-9.

67. Eiden LE, Weihe E. VMAT2: a dynamic regulator of brain monoaminergic neuronal function interacting with drugs of abuse. Annals of the New York Academy of Sciences. 2011;1216(1):86-98. doi:10.1111/j.1749-6632.2010.05906.x.

68. Takahashi N, Miner LL, Sora I, Ujike, H., Revay, R. S., Kostic, V. et al. VMAT2 knockout mice: Heterozygotes display reduced amphetamine-conditioned reward, enhanced amphetamine locomotion, and enhanced MPTP toxicity. Proceedings of the National Academy of Sciences. 1997;94(18):9938-9943. doi:10.1073/pnas.94.18.9938.

69. Baumann A, Moreira CG, Morawska MM, Masneuf S, Baumann CR, Noain D. Preliminary Evidence of Apathetic-Like Behavior in Aged Vesicular Monoamine Transporter 2 Deficient Mice. Frontiers in Human Neuroscience. 2016;10. doi:10.3389/fnhum.2016.00587.

70. Chu TT, Liu Y. An integrated genomic analysis of gene-function correlation on schizophrenia susceptibility genes. Journal of Human Genetics. 2010;55(5):285-292. doi:10.1038/jhg.2010.24.

71. Berg KA, Harvey JA, Spampinato U, Clarke WP. Physiological relevance of constitutive activity of 5-HT2A and 5-HT2C receptors. Trends in Pharmacological Sciences. 2005;26(12):625-630. doi:10.1016/j.tips.2005.10.008.

72. Millan MJ. The Novel Melatonin Agonist Agomelatine (S20098) Is an Antagonist at 5-Hydroxytryptamine2C Receptors, Blockade of Which Enhances the Activity of Frontocortical Dopaminergic and Adrenergic Pathways. Journal of Pharmacology and Experimental Therapeutics. 2003;306(3):954-964. doi:10.1124/jpet.103.051797.

73. Stefanis L. -Synuclein in Parkinsons Disease. Cold Spring Harbor Perspectives in Medicine. 2011;2(2). doi:10.1101/cshperspect.a009399.

74. Braak H, Tredici KD, Rüb U, Vos RAD, Steur ENJ, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiology of Aging. 2003;24(2):197-211. doi:10.1016/s0197-4580(02)00065-9.

75. Błaszczyk JW. Parkinsons Disease and Neurodegeneration: GABA-Collapse Hypothesis. Frontiers in Neuroscience. 2016;10. doi:10.3389/fnins.2016.00269.

76. Ephraty L, Porat O, Israeli D, Cohen, OS, Tunkel O, Yael S. et al. Neuropsychiatric and cognitive features in autosomal-recessive early parkinsonism due to PINK1 mutations. Movement Disorders. 2007;22(4):566-569. doi:10.1002/mds.21319.

77. Scott S, Abul-Husn N, Obeng AO, Sanderson S, Gottesman O. Implementation and utilization of genetic testing in personalized medicine. Pharmacogenomics and Personalized Medicine. 2014:227. doi:10.2147/pgpm.s48887.

78. Lohmann E, Welter M-L, Fraix V, et al. Areparkinpatients particularly suited for deep-brain stimulation? Movement Disorders. 2008;23(5):740-743. doi:10.1002/mds.21903.

79. Kasten M, Hartmann C, Hampf J, Schaake S, Westenberger A, Vollstedt E. et al. Genotype-Phenotype Relations for the Parkinsons Disease Genes Parkin, PINK1, DJ1: MDSGene Systematic Review. Movement Disorders. 2018;33(5):730-741. doi:10.1002/mds.27352.

80. Ivanets N.N., Kinkulkina M.A., Tikhonova Yu.G. et al. Association of serotonin and dopamine transporters genes (SLC6A4, SLC6A3) polymorphisms with tolerance of different classes of antidepressants. Psychiatry and psychopharmacotherapy. 2015; 17(3): 13–21.

Corresponding author
Ragimova Aynur
ragimovaasia@gmail.com

No conflict of interest stated.

Doi 10.26269/d6gp-4t10

Left ventricular hypertrophy of arterial hypertension in patients with CHD is associated with polymorphism of the tumor necrosis factor gene

L.O. Minushkina[1], V.A. Brazhnik[1,2], N.D. Selezneva[1,2], O.S. Chumakova[1], M.A. Evdokimova[1], R.R. Guliev[3], G.I. Speshilov[4], D.A. Zateyshchikov[1,2]

[1]Central State Medical Academy of Department of Presidential Affairs, Moscow, Russia,
[2]City Clinical Hospital No. 51, Moscow, Russia,
[3]Institute of Biochemical Physics N.M. Emanuel Russian Academy of Sciences, Moscow, Russia,
[4]Genome Center "ReadSense", Russia

Abstract

The aim of the study was to study the possible association of the polymorphic variant G (-308) A of the tumor necrosis factor alpha (**TNF**) gene with the structure and function of the myocardium in patients with arterial hypertension (**AH**) and coronary heart disease (**CHD**). Patients were selected for the study from those included in the observation programs of ORACLE I and II (*ORACLE - ObseRvation after Acute Coronary syndrome for deveLopment of trEatment options*). A total of 875 patients with hypertension were examined, with an average age of 62.7 ± 12.57 years (*531 men (60.8%) and 344 women (39.2%)*).

In the examined group, there were 137 (15.8%) patients suffering from type 2 diabetes mellitus, 645 (73.7%) with a history of coronary artery disease before inclusion in the study, 78 (9.0%) suffered a stroke, 519 (59.3 %) had hypertension of 3 severities. The frequency distribution of alleles and genotypes of the **TNF gene** (AA - 7 patients (0.7%), **AG genotype** - 237 patients (27.1%), **GG genotype** - 631 patients (72.1%) differed from those expected by Hardy-Weinberg equation by reducing the frequency of the rare homozygous genotype: chi-square 9.87, p <0.005. In patients with **LVH**, the frequency of the **GG genotype**, *allele G and the frequency of allele A of the TNF gene* were significantly lower. Allele A carriers in the homo- and heterozygous state had a greater **LVMI**, a lower left ventricular ejection fraction, and a ratio of peak rates E and A. In a multifactorial regression analysis, the male gender, the level of systolic pressure, the age of patients, and the presence of genotype allele A of the **TNF gene**.

Key words: arterial hypertension, left ventricular myocardial hypertrophy, tumor necrosis factor, gene, polymorphism.

The tumor necrosis factor alpha (**TNF**) is one of the pro-inflammatory cytokines involved not only in the regulation of inflammation, but also influencing the formation of insulin resistance, activation of the renin-angiotensin system (**RAAS**) and the activation of growth factors. Shown, that increased tumor necrosis factor is associated with an increase in cardiovascular risk. It is known that this factor is associated not only with the formation of the immune response, but also the development of atherosclerosis, endothelial dysfunction, insulin resistance, coagulation disorders. Experimental evidence of the involvement of tumor necrosis factor alpha in the development of left ventricular hypertrophy (**LVH**) in animals has been found [1]. At the same time, **LVH** in patients with cardiovascular diseases is an additional risk factor for adverse outcomes. This determines the interest in the pathogenic mechanisms of LVH development, in particular, associated with the activation of the inflammatory system. The expression of **TNF** is largely determined by genetic factors, one of the variants of which is the **polymorphism G (-308) A**, which is located in the region of the gene promoter. In this regard, the goal of our study was to examine the possible association of the **polymorphic variant G (-308) A** of the tumor necrosis factor **alpha (TNF)** gene with the structure and function of the myocardium in patients with arterial **hypertension (AH)** and coronary heart disease (**CHD**).

Material and research methods

Patients were selected for the study from those included in the observation programs of ORACLE (*ORACLE - ObseRvation after Acute Coronary syndrome for deveLopment of trEatment options*) - ORACLE I (2004-2009) and ORACLE II (2014-2018). A total of 2695 patients who had an episode of acute coronary syndrome were observed in the studies. To assess the association of the parameters of the structure and function of the myocardium and **TNF gene polymorphism**, 875 patients with hypertension were selected, who underwent an echocardiographic study, as well as those who did not tolerate large-focal myocardial infarction and did not have valvar heart disease. *The average age was 62.7 ± 12.57 years (531 men (60.8%) and 344 women (39.2%)), 137 (15.8%) patients had type 2 diabetes, 645 (73.7 %) had a history of coronary artery disease before inclusion in the study, 78 (9.0%) suffered a stroke, 519 (59.3%) had AH 3 severity.*

In an echocardiographic (*EchoCG*) study in M-mode at the level of the chords of the mitral valve from

the parasternal access, the end-diastolic (CCD), the final systolic size (CCP), the thickness of the interventricular septum (TMV) and the thickness of the posterior wall of the left ventricle (TSSL). The mass of the myocardium of the left ventricle (MLM) was calculated *by the formula R. Devereux and N. Reichek, 1977* [2]:

$$1.04\times\{(TMZHP+TZSLZh+KDR)^3-KDR^3\}-13.6.$$

The left ventricular myocardial mass index (LVMI) was calculated as the ratio of left ventricular myocardial mass to body surface area (Cornell criterion: 115 g /m^2 was considered the upper limit of normal for men and 95 g / m^2 for women).

The global diastolic function of the left ventricle was assessed by trans-mitral blood flow using pulse wave Doppler echocardiography from the apical access at the four-dimensional position with the position of the control volume at the ends of the mitral valve cusps. The following indicators were determined: the maximum speed of the early (Amax) filling of the LV, the maximum speed of the late (Amax) filling of the LV, their E / A ratio, and the time of isovolumetric relaxation (IVRT) of the LV.

The determination of the alleles and genotypes of the TNF gene was performed using PCR. We used 2.5x PCR-RV reaction mixture containing SynTaq DNA polymerase with antibodies inhibiting the activity of the enzyme (CJSC Syntol, Moscow). Oligonucleotide primers were synthesized by Evrogen (Moscow). Genomic DNA was isolated from whole blood of patients by the method of extraction with a mixture of phenol and chloroform after incubating blood samples with proteinase K in the presence of 0.1% sodium dodecyl sulfate.

Alleles of polymorphic markers were identified using hybridization-fluorescence analysis (TaqMan® analysis) on a Bio-Rad CFX96 C1000 Touch real-time amplifier (Bio-Rad Laboratories, Inc., USA) in 25 µl of the reaction mixture of the following composition: 2.5x Reaction mixture for PCR-RV, 4 pcol of each primer and probe, 25 ng of genomic DNA.

Conditions for amplification of the DNA fragment: pre-denaturation of 95 ° C / 2 min, 95 ° C / 10 s, 60 ° C / 60 s - 40 cycles. The composition of primers and probes are presented in table 1.

Statistical data processing was carried out using the SPSS 23.0 program. For extended indicators, an analysis was made of the distribution and criteria for its compliance with the normal one. Since the distribution of all the studied parameters corresponded to the normal, parametric calculation methods were used for the analysis. For extended variables, the mean values and standard deviation from the mean ($M \pm SD$) were calculated. To assess the significance of differences in the means used t-test. Discrete values were compared by

Table 1

Used primers and probes

Primer	Allele	Sequence
Straight	-	TGGAAGTTAGAAGGAAACAGAC
Back	-	ACACAAGCATCAAGGATACC
Probe 1	G	FAM-CCGTCCCCATGCCC-BHQ1
Probe 2	A	HEX-CCGTCCTCATGCCC-BHQ1

Pearson criterion χ_2. To assess the independence of the influence of various factors on myocardial hypertrophy, logistic regression was used. Parameters that demonstrated statistical significance in a single-factor analysis were included in the multivariate analysis. For all types of analysis, p <0.05 was considered statistically significant.

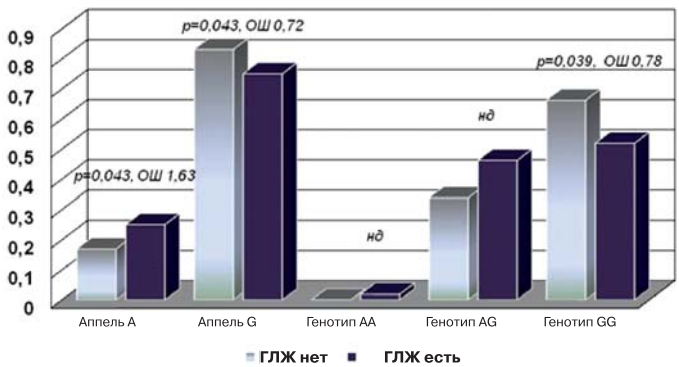
The correctness of the distribution of genotype frequencies was determined by matching the Hardy-Weinberg equilibrium (pi2 + 2pipj + pj2 = 1) and was calculated using the Gen Expert Expert software calculator.

Results

The frequency distribution of alleles and genotypes of the TNF gene (AA - 7 patients (0.7%), AG genotype - 237 patients (27.1%), GG genotype - 631 patients (72.1%) differed from those expected by Hardy-Weinberg equation by reducing the frequency of the rare homozygous genotype: chi-square 9.87, p <0.005.

In total, 400 patients in the examined group had LVH. In this group there were more men. Patients with LVH were older in age, had a higher level of systolic blood pressure (BP), more often circulatory insufficiency was recorded. Patients with LVH had a lower level of glomerular filtration rate (Table 2).

Carriers of allele A in the homo and heterozygous state had a greater LVMI, a lower left ventricular ejec-



Legend: On "X": Allele A; Allele G; AA genotype; GA genotype; GG genotype;
The dark blue color marks the existence of: *LVH - left ventricular hypertrophy. The light blue color marks the inexistence of:* LVH - left ventricular hypertrophy.
Figure 1. Frequency distribution of genotypes of the TNF gene in patients with and without LVH.
TNF - tumor necrosis factor alpha;
LVH - left ventricular hypertrophy;

Table 2

Clinical characteristics of patients with dependence on the presence of LVH

Options	Patients without LVH (*n*=475)	Patients with LVH (*n*=400)	*R*
Sex : Male/ Female	278/197 (58/41%)	253/147 (67/33%)	0,046
Age years	58,2±1,35	64,8 ±1,02	0,001
Type 2 diabetes, *n* (%)	66 (14,1)	71 (17,8)	нд
Duration GB (years)	13,1 ±1,29	13,3±1,09	нд
BMI, kg / m^2	28,7±0,47	28,3±0,33	нд
Maximum systolic blood pressure, mm.rt.st.	184,1± 3,3	195,3 ± 2,86	0,01
Maximum diastolic blood pressure, mm.rt.st.	103,5 ±2,17	108,1 ±1,45	нд
Circulatory failure, *n* (%)	197 (42%)	227 (52%)	0,001
GFR (MDRD), ml / min / 1.73 sq.m.	64,8±16,79	60,9±18,78	0,005

LVH - left ventricular hypertrophy; GB hypertensive disease; Arterial blood pressure; GFR-glomerular filtration rate.

Table 3

Parameters of the structure and function of the myocardium of the left ventricle in patients with different genotypes of the polymorphic marker G (-308) A of the TNF gene

Options	GG genotype	GA genotype	AA genotype	*R*
TMZHP, mm	12,13±2,478	11,49±5,187	13,14±7,714	нд
TZSLZH, mm	10,88±1,512	11,07±5,095	11,57±4,434	нд
CRD LV, mm	47,25±4,528	49,55±7,575	50,14±9,139	нд
The diameter of the aortic root, mm	25,87±6,756	28,00±6,565	27,50±6,164	0,037
Diameter PL, mm	38,84±6,119	38,60±5,532	37,50±6,547	нд
EF LV,%	62,67±10,619	58,00±11,650	56,55±11,848	0,001
MLW, g	253,1±59,237	259,3±82,76	270,9±93,19	нд
LVMI, g / m	131,35±31,079	139,74±53,514	151,65±41,313	0,020
E_{max}, m / s	89,10±3,618	71,96±2,114	55,86±17,582	0,021
A_{max}, m / s	76,91±2,2025	77,26±5,122	57,86±10,447	нд
E / A ratio	1,36±0,927	1,04±0,554	0,99±0,356	0,013

TMZH-thickness of the interventricular septum; TZSLZh- thickness of the posterior wall of the left ventricle, LVC LV, of course, the diastolic size of the left ventricle; LP - left atrium; EF LV-left ventricular ejection fraction; MLJ is the mass of the myocardium of the left ventricle; LVMI index of myocardial mass of the left ventricle.

tion fraction, and a ratio of peak velocities E and A (Table 3). Thus, the carriage of allele A in the hetero- and homozygous state was associated with left ventricular myocardial hypertrophy, as well as with the formation

Table 4

Regression analysis of the independence of the association of clinical factors with LVH in patients with hypertension

Factors	Univariate analysis		Multivariate analysis	
	OR [95% CI]	*r*	OR [95% CI]	*r*
Male	2,28[1,66-3,13]	0,001	1,54 [1,02–2,03]	0,048
Age over 60 years	2,62[1,92-3,59]	0,001	1,71 [1,34–2,28]	0,01
CAD> 180 mmHg	2,20[1,57-3,07]	0,002	1,86 [1,22–2,64]	0,002
Circulatory failure	2,44[1,81-3,30]	0,001	1,76[0,96-2,58]	0,053
СКФ (MDRD)<60 мл/мин/1,73 м2	1,76[1,03-2,28]	0,039	1,12[0,86-2,48]	0,086
Carriage of allele A of the polymorphic marker A (-308) G of the gene TNF	2,36[1,09-4,93]	0,005	1,97 [1,12–2,89]	0,003

LVH - left ventricular hypertrophy; Hypertension - arterial hypertension; Systolic blood pressure; GFR-glomerular filtration rate.

of left ventricular diastolic dysfunction and a decrease in myocardial contractility.

Considering the differences in the main clinical characteristics of groups of patients with and without LVH, one-factor and multifactorial regression analysis of the association of clinical factors and the TNF gene genotype with the development of LVH was conducted (Table 4). For inclusion in the regression analysis, extended factors (age and level of MAP) were converted to discrete ones. By age, patients are divided into 2 groups according to the median indicator (60 years). According to the maximum level of blood pressure, patients are divided into groups according to the level corresponding to hypertension of 3 degrees (above and below 180 mm Hg). In a multifactorial regression analysis, the male gender, systolic pressure, age of patients, the presence of the TNF gene A allele in the genotype were independently associated with an increase in LVMI.

The discussion of the results

The possible association between the activation of inflammation processes and the formation of myocardial hypertrophy is actively discussed in the literature. The involvement of TNF in the formation of myocardial hypertrophy is confirmed by a number of clinical and experimental data. In a study on a group of 764 patients with hypertension, it was shown that the levels of TNF and IL-6 are more significant predictors of the development of concentric remodeling and concentric left ventricular hypertrophy than hemodynamic factors, and systolic blood pressure in particular. The level of blood pressure to a greater extent determined the increase in myocardial mass [3].

In patients with hypertrophic cardiopathy, a significantly higher level of tumor necrosis factor, IL-6 and serum amyloid P is registered compared with comparable healthy controls. At the same time, in patients with local myocardial fibrosis, the level of interleukins 1 and 4 is higher, as well as matrix metalloproteinase, which indicates different mechanisms for the development of these diseases [4]. In a group of patients with Fabry disease with a significant increase in the level of TNF, expression of TNF receptors was shown to associate the level of these markers with the severity of myocardial hypertrophy and the formation of diastolic myocardial dysfunction, as well as an increase in BNP and a heart failure clinic [5].

In experiments on mice, it was shown that an increase in the expression of TNF and its receptors may trigger the formation of hypertrophic cardiopathy and myocardial hypertrophy of aortic stenosis [6]. Experimental animals also showed a strong association between the level of cycling TNF and the activation of myocardial fibrosis and kidney processes in animals with elevated blood pressure [7].

The association between the development of myocardial hypertrophy and an increase in the level of tumor necrosis factor is explained by the fact that TNF enhances the effect of angiotensin II on the expression of various growth factors. This mechanism is mediated by the presence of a common signaling pathway for TNF and anti-tensin II. This signaling pathway is also associated with the mechanisms of antioxidant protection and includes mitogen-activated protein kinase, transforming growth factor beta1 and nuclear factor Kappa-B. (MAPK / TGF-β / NF-κB). A similar mechanism of interaction between TNF and RAAS has recently been confirmed in animal experiments [8].

In our study, we did not evaluate the plasma level of TNF, but used a genetic marker in the TNF gene associated with changes in the expression of factor.

The TNF gene is mapped in the chromosomal region 6p23-q12. One of the most interesting polymorphic variants of a gene is the replacement of G (-308) A, which is localized in the promoter of the gene. Associations of the rare A allele of this polymorphic variant with bronchial asthma, psoriatic arthritis and systemic lupus erythematosus are shown [9, 10, 11].

There is a lot of data on the association of the polymorphic marker G (-308) A with the risk of coronary complications [12]. Similar data were obtained, including by our group, in the framework of a multicenter observational study of ORACLE [13]. We also studied the association between the polymorphism of this gene and myocardial changes in patients with aortic stenosis, but no association was found [14].

There is evidence in the literature about the association of the A allele of the polymorphic marker G (-308) A of the TNF gene with the development of gestational hypertension and preeclampsia, obtained on a group of 1,623 pregnant women [15]. Also of interest are data on the association of allele A with the level of systolic blood pressure and the level of insulin in blood plasma in patients with metabolic syndrome, obtained in a meta-analysis that includes more than 800 patients [16]. There are data on the association of the carriage of allele A with the risk of developing diabetic nephropathy [17].

In our study, we showed for the first time the association of the A allele of the polymorphic marker G (-308) A of the TNF gene with the development of myocardial hypertrophy in patients with arterial hypertension and the formation of diastolic and systolic myocardial dysfunction. These data confirm the possible role of the TNF signaling pathway in the formation of myocardial changes and create prerequisites for further research.

Corresponding author
Minushkina Larisa
minushkina@mail.ru

No conflict of interest

Information about authors:

Minushkina L.O. - Professor of the Department of Therapy, Cardiology and Functional Diagnostics with a course of nephrology at the Central State Medical Academy, minushkina@mail.ru, author for correspondence

Brazhnik Victoria Alekseevna FGBU Candidate of Medical Sciences, Associate Professor of the Therapy, Cardiology and Functional Diagnostics Department of the FSBE DPO Central State Medical Academy of the Presidential Administration of the Russian Federation, Moscow 121359, ul. Marshal Timoshenko, 19, p.1A, vabrahznik@bk.ru, +74991464151

Chief Physician, City Clinical Hospital No. 51 DZ, Moscow, 121309, Moscow, ul. Alyabiev d7 / 33, +7 (499) 146-82-94

Natalya Dmitrievna Selezneva PhD, Assistant Professor, Department of Therapy, Cardiology and Functional Diagnostics, FSBE DPO Central State Medical Academy of the Presidential Administration of the Russian Federation, Moscow 121359, ul. Marshal Timoshenko d.19, p.1A, nsel@yandex.ru, +74991464151

Head Department of Functional Diagnostics GBUZ "City Clinical Hospital №51 DZ g Moscow", Moscow, 121309, st. Alyabiev d7 / 33, +7 (499) 146-82-94

Chumakova Olga Sergeevna Ph.D., Associate Professor of the Therapy, Cardiology and Functional Diagnostics Department of FSBE DPO Central State Medical Academy of the Office of the President of the Russian Federation, Moscow 121359, ul. Marshal Timoshenko, 19, p.1A, chumakovaolga@bk.ru, +74991464151

Marina Andreevna Evdokimova, doctor, City Clinical Hospital No. 51, Moscow DZ, Moscow, 121309, ul. Alyabieva d7 / 33, onlygarbagecan@list.ru +7 (499) 146-83-05

Rustam Guliev, Researcher, Institute of Biochemical Physics N.M. Emanuel Russian Academy of Sciences, 119334, Moscow, st. Kosygin, 4, +7 (495) 939-7439, glvrst@gmail.com

Gleb Speshilov, Researcher, Federal State Budgetary Institution of Science A.A. Kharkevich of the Russian Academy of Sciences (IITP RAS), head of the genetic laboratory of the Genome Center "ReadSense", g.speshilov@chromaspark.com

DA Zateyshchikov, MD, Professor, Head of the Department of Therapy, Cardiology and Functional Diagnostics, Central State Medical Academy, Office of the President of the Russian Federation, Moscow 121359, ul. Marshal Timoshenko d.19, p.1A, head of the primary vascular department of the City Clinical Hospital №51 DZ g of Moscow, Moscow, 121309, ul. Alyabiev d7 / 33, dz@bk.ru, +7 (499) 146415

Doi 10.26269/pzq2-p709

The problem of compliance in psychiatry

I.V. Belokrylov, V.P. Sokolov
Department of psychiatry and medical psychology Peoples' Friendship University of Russia, Moscow

Abstract
The article presents an overview of major Russian and foreign literature on the problems of compliance in patients with schizophrenia. The article describes key factors associated with the patient's refusal of the prescribed treatment. The article describes the basic methods of evaluation of compliance: experimental and psychological, with applied clinical significance. The article describes the main factors associated with the patient's refusal of the prescribed treatment, describes the contribution of low compliance not only to the patient's quality of life, but also to the health care costs associated with repeated hospitalizations of non-compliant patients. The article examines methods for overcoming non-compliance in patients with schizophrenia, for example, compliance therapy — a psychotherapeutic method that is short-lived, convenient and simple to use in clinical practice, and has shown rather high efficiency.
Key words: psychiatry, schizophrenia, compliance, mental disorders, psychopharmacotherapy.

Introduction

The term "compliance" means patient's voluntary adherence to the prescribed treatment, correctness and adequacy of compliance with medical recommendations.

Compliance with the medical regimen prescribed by a doctor is an urgent research task in almost all areas of clinical medicine. For example, about 40% of hypertensive patients discontinue antihypertensive therapy, and in 25% of cases, self-abolition of supportive treatment occurs already within six months after the start of treatment. Compliance is of particular importance in psychiatry. Many researchers state that the degree of adherence to therapy in patients with mental disorders is significantly lower than in somatic patients, especially in conditions of long-term, long-term medication [1]. For example, for patients with schizophrenia, an increased risk of recurrence and re-hospitalization is the most significant clinical consequence of non-compliance with prescribed medication for schizophrenia. According to the results of studies conducted by American and British psychiatrists, out of 1,646 patients with schizophrenia, 58.6% stopped taking maintenance therapy for 3 months after discharge from the psychiatric hospital, which later became the cause of recurrences of psychopathological symptoms and repeated hospitalizations. In another randomized study [2], incomplete adherence to the treatment regimen was reported, 57.5% of 876 examined patients with schizophrenia experienced episodes of self-dose adjustment, up to and including the complete rejection of drugs due to "good health". According to researchers from San Diego [3], (a sample of 2,801 people) in non-treatment patients there was a 2.5-fold increase in the frequency of re-admissions to psychiatric hospitals compared with compliant patients. Thus, a low degree of compliance in patients suffering from mental illness contributes to a more severe course of the disease and has a negative impact on the quality of life. [four]. At the same time, patients who observed the correct dosage of the drug and complied with all the prescriptions of the attending physician had a significantly lower risk of re-admission to a psychiatric clinic.

In addition to its purely clinical implications, low compliance significantly increases the costs of the health care system. According to Western studies, due to low adherence to drug treatment of patients with schizophrenia, the workload of one of the clinics increased by 1,21838 bed-days, which corresponds to expenditures of 106 million US dollars [5]. According to researchers from Florida [6], obtained on a sample of 10,330 patients with schizophrenia, there was a marked inverse correlation between patient compliance and the costs of the health care system. Costs for patients with little adherence to treatment were significantly higher than for compliant patients. Against the background of low compliance, monotherapy with atypical antipsychotics increased costs of $ 133, monotherapy with typical antipsychotics increased by $ 294, and during combination therapy with typical and atypical antipsychotics, expenses increased by $ 221. In a San Diego study, outpatient treatment costs were significantly higher for non-compliant patients than for compliant patients, although overall costs were higher for patients with high adherence due to increased pharmacy costs. In a UK survey of 628 patients receiving antipsychotic drugs, failure to comply with the treatment regimen was associated with an increase in inpatient treatment costs of approximately 2,500 pounds per year, which increased costs up to 5,000 pounds per patient per year [7].

Compliance factors

The main difficulty arising in the study of compliance is determined by the multifactor nature of this phenomenon. At present, over two hundred factors have been identified that in one way or another determine the attitude of patients to maintaining the therapy regimen [8]. Compliance reflects the complex interaction of these factors, the configuration of which varies in the dynamics of the disease and at remote stages may differ significantly from the initial one. With regard to schizophrenia, compliance factors can be divided into the following groups:

1) factors associated with drug treatment (in particular, side effects of drugs, the need to comply with the regimen);

2) factors associated with productive symptoms of the disease;

3) factors associated with negative symptoms of the disease, including cognitive disorders;

4) factors associated with the attending physician, his professionalism and ability to maintain optimal psychological contact with the patient (therapeutic relationship);

5) social and micro social factors.

It is very difficult to determine the significance of the whole diversity of these factors and the nature of their influence on compliance. It seems more expedient to single out the most significant, main factors of compliance, to study the mechanisms of their impact on the phenomenon and to develop measures aimed at correcting them and at increasing compliance.

An important aspect of compliance in relation to psychopharmacotherapy is the tolerability of drugs, the patient's reaction to the side effects associated with taking drugs, the complex of objective neurophysiological as well as subjective individual psychological sensations that arise. Typical neuroleptic drugs with a relatively high level of their therapeutic efficacy have hardest tolerance. The main pharmacological side effects of psychotropic drugs are extrapyramidal neurological disorders, endocrine disorders leading to an increase in body weight, decreased libido, etc., as well as excessive drug sedation.

In order to improve compliance and the quality of life of patients with chronic mental disorders, in the 1960s, the deposited forms of traditional neuroleptics were synthesized and introduced into medical practice. The use of these agents in some cases improved compliance, but they also had side effects typical of the corresponding oral forms [9,10]. Recently, in the development of new psychotropic drugs, its compliant properties were determined as one of the main parameters of the final product [11]. In line with this trend, so-called atypical antipsychotics were synthesized. Among their side effects, at least, extrapyramidal disorders are less frequent (although endocrine disorders are no less frequent than in typical ones) [12]. One of the latest achievements of psychopharmacology was the creation of atypical antipsychotics with prolonged action, like traditional prolonged neuroleptics [13]. However, psychotropic drugs of the most modern classes also show side effects, leading to a decrease in the level of adherence to therapy. Therefore, the best compliance, as a rule, provides an adequate dosing regimen with the selection of the minimum sufficient dose [14]. However, a direct correlation between the low level of compliance and the side effects of drugs has not been established. According to some data, at the stage of initial stabilization of remission, higher dosages of neuroleptics and, consequently, a greater manifestation of extrapyramidal side effects may be accompanied by good compliance [15].

Factors that adversely affect the performance of medical appointments can be uncomfortable or difficult for patients to administer drugs, for example, the need to take the drug several times a day, as well as the high cost of self-medication.

A variety of clinical factors, such as psychopathological symptoms, comorbid symptoms, different course options, progression of the disease, options for drug and other pathomorphosis, which determine the level of adherence of mentally ill patients to the prescribed therapy regimen, have been repeatedly discussed in the medical literature. Researchers have found a large number of correlates of manifestations of mental illness with a level of compliance [16].

An important criterion for evaluating compliance is the adequacy of judgments about one's own illness. The patient's proper understanding of the nature of his own disease, its manifestations and consequences, as well as the consistency of the patient's ideas about his own illness with accepted medical and social criteria is called the awareness of mental illness [17].

It is a violation of the awareness of mental illness is considered one of the pathognomonic criteria of many mental disorders, including schizophrenia. The concept of anosognosia is widespread, which consists in denying the existence of the disease. In particular, the well-known phenomenon of alcohol anosognosia - the denial of alcohol dependence. In this category of patients, anosognosia is the main, determining component of the attitude towards the disease. Initially, alcohol anosognosia was considered as a consequence of psychoorganic syndrome and alcoholic personality changes, and later it was interpreted as manifestations of the psychological defense system [17].

In clinical practice, the phenomenon of awareness of mental illness is identified with the concept of "criticality." However, the term “criticality” has insufficient methodological development, since there is no precise

definition of criticality, despite the frequent use of this concept.

There are several aspects of this concept.

The first is criticism of one's judgments, actions, and statements. This type of criticality is an important characteristic of thinking. The second is self-criticalness, to the assessment of one's personality. This component of criticality implies the understanding by the patient of his place and role in life, his strengths and weaknesses. The third aspect is criticality to one's own psychopathological experiences. This form of criticality is considered in psychiatry as an indicator of the positive dynamics of the disease and the criterion of remission. Thus, it is the criticality to their psychopathological experiences that describes the phenomenon of awareness of mental illness. Violations of criticality can be in the form of unfocused actions, judgments, violations of the prediction of their actions, as a result of which the patient loses the ability to correct his behavior, which in turn affects the patient's compliance and adherence to the doctor's prescriptions.

At the same time, the concept of "criticality" has significant limitations for the clinical evaluation of a patient's thinking disorder. For example, the main drawback is the monotony of the awareness of the disease, since the criticality is considered only the patient's ability to recognize the pain of their own symptoms. In clinical practice, psychiatrists usually assess not only the criticality for manifestations of the disease, but also a number of other criteria, such as criticality for the causes of the disease, the need for treatment, and others. However, due to the lack of diagnostic standards for evaluating criticism, this phenomenon is difficult to apply for evaluating compliance.

Cognitive impairments in mentally ill patients are also highlighted by the authors in terms of the problem of compliance [18]. Errors in taking medications and side effects of drugs can be largely a consequence of the patient's inability to read and understand written and oral instructions. The problem is not limited to the fact that patients must read the printed material or hear the information spoken by a doctor. They are required to understand, realize, keep in memory and apply this information in life, changing their behavior, bad habits, lifestyle, etc., if necessary. This ability may be several orders of magnitude lower than the ability to simply read the material. In this regard, studies of prospective memory (the ability to remember what needs to be done in the future) and drug management in adult patients with schizophrenia and schizoaffective disorder are of interest. Negative changes, the severity of the emotional-volitional personality defect correlated in these patients with a lower ability to follow the regimen of drug therapy. Impaired cognitive functions in these studies were a more significant predictor of non-compliance with the treatment regimen than, for example, the severity of productive symptoms and attitudes toward treatment [19].

Social factors also significantly affect the compliance of the mentally ill, since they largely determine the patient's attitude towards psychiatric treatment and adherence to treatment, his motivation for treatment or a negative attitude towards him. The key role is played by the patient's microsocial environment - the family. According to American and British researchers, the involvement of the patient's family in the formation of compliance is extremely high, so holding family meetings with a doctor is an essential condition for the effectiveness of measures to improve it.

The psychiatrist is the main component of the treatment and rehabilitation system to a large extent due to his ability to ensure compliance. He not only acts as a passive mediator between the patient and the medical arsenal available in medicine, but builds a personalized system of relations with the patient, is a highly active figure determining the patient's participation in the therapeutic process. Not only patient's understanding of the treatment benefits, but also the doctor's attentiveness to all the problems of the patient contributes to full compliance [20].

A necessary basic condition for achieving good patient compliance is the qualifications of a doctor. According to S.N. Mosolov [11], about 50% of cases of ineffectiveness of therapy are associated with its inadequate administration. The most common mistakes, in addition to the late initiation of treatment and non-observance of clinical indications and contraindications, are the holding of a template (without taking into account individual features) low-dose therapy, frequent drug changes without observing the desired duration of treatment, premature discontinuation of therapy, simultaneous administration of a large number of drugs (polypragmasy) [21].

In the long-term treatment conditions, continuous and effective medical alliance of a doctor with a patient has particular importance. To achieve trust, mutual understanding and proper contact with the attending physician, interested participation of the patient in the process of therapy means minimizing violations of the prescribed recommendations. In a number of publications devoted to this issue [22], the need to properly build a dialogue with the patient is emphasized. The most important conditions are time and patience on the part of the physician. It is necessary to conduct explanatory work with the patient, explain the reasons for his illness, emphasize the need for long-term and regular treatment. These aspects of compliance can be combined with the concept of psychotherapeutic, appealing to the problems of the subjective picture of the disease,

the personality-mediated attitude of the patient to the symptoms and therapeutic measures [23].

Unfortunately, doctor-patient communication often is formal, a doctor does not care about adequate amount of information offered to a patient. The situation is complicated by the fact that nowadays patients are actively using the Internet, which often offers distorted information about mental disorders, medications and their side effects. In combination with the psychotherapeutic inaction of a doctor, this greatly enhances the stigmatization of a patient, causes him unfounded fears in connection with a treatment and worsens compliance. These trends are particularly relevant in modern conditions of modernization of the psychiatric service, which envisages the reduction of the inpatient stage with an increase in the proportion of semi-inpatient and outpatient forms of treatment, with the inevitable increase in the responsibility of the patient's family for taking medications and observing other aspects of the treatment regime.

Compliance assessment methods

The independent vector of modern compliance research is aimed at predicting adherence to treatment. Patient compliance is established when re-admitted to a psychiatric hospital; As a reliable method for its assessment, the most commonly used measurement is the concentration of the drug in the blood. The publications deal with such methods for evaluating compliance, such as a microelectronic monitoring system embedded in the cap of the drug package [24]. While doctors estimate that 95% of patients were compliant, the electronic system showed that only 38% of them followed the therapy regimen. There is evidence of the use of the riboflavin marker method, which was added to the study drug and to placebo. Riboflavin fluoresces when irradiated with ultraviolet light, which makes it easy to carry out rapid control of its content in the urine and thereby control the administration of prescribed drugs [25,26].

However, all these methods are not applicable for mass use in clinical practice, therefore, to study compliance, indirect methods are used, mainly specific psychometric scales.

In American clinical practice, the setting scale for DAI treatment (Disease Attitude Inventory) is used. The Morisky compliance scale is a very popular and widely used in somatic medicine. In 2012, the St. Petersburg Bekhterev Psychoneurological Research Institute developed the scale of drug compliance (SDC) [4].

Clinical and psychological research can be used to assess compliance in a psychiatric clinic, in which compliance is measured by evaluating the awareness level of a mental disorder in a patient, which is assessed using an interval scale containing indicators of low, partial and complete insight (awareness of the disease). Currently, there are several valid and insight assessment methodologies, which are semi-structured interviews [27,28].

Scale to Assess the Unawareness of Mental Disorder is designed specifically to assess the awareness of the disease in patients with mental disorders, particularly schizophrenia. This scale makes it possible to evaluate the above-mentioned aspects of criticality, to evaluate the parameters of awareness, and understanding of the causes in the time perspective of the patient's present and past state. The assessment is made on the basis of the clinical conversation data on a five-point scale, where the lowest score corresponds to the highest level of insight [17]. This technique is widely used in scientific and clinical studies, which expands the possibilities of comparison and discussion of the results. Other examples of methods for assessing insight in a semi-structured interview include The Insight and Treatment Attitudes Questionnaire (ITAQ) and The Schedule for the Assessment of Insight-Expanded (SAI-E).

Methods to improve compliance

Along with the pharmacological method of improving compliance, which is the most accessible for a practicing psychiatrist, which consists in conducting rational psychopharmacotherapy, prescribing drugs that are optimal for each patient and their doses, avoiding polypragmasy, many authors agree on the need to include other specialists in the process psychiatrist), as well as enhancing the role of nursing staff of medical institutions [29,30].

In order to improve patient compliance with the treatment regimen, various techniques are used, including psycho-education, family therapy, behavioral therapy, and psycho-pedagogical techniques. A method of psychotherapeutic correction of compliance, called compliance therapy, using cognitive-behavioral technologies has been developed; The latter combine motivational interviews with active therapeutic attitudes, problem solving, and educational cognitive components [31,32].

The method of compliance therapy was originally developed for the treatment of patients suffering from drug and alcohol addiction as an auxiliary method designed to improve the quality of remission. R. Kemp et al. adapted the method of compliance therapy for the treatment of patients with acute psychotic states [33]. The advantages of compliance therapy are short-term (it takes from 6 to 12 psychotherapeutic sessions), practical orientation and expansion of goals, from the task of following the psychopharmacotherapy regimen to a wider adherence to all medical recommendations in clinical practice. Thus, it is a practical and easily implementable intervention in real clinical conditions. In recent years, foreign and domestic researchers obtained data on the effectiveness of this technique. Psychotherapeutic ses-

sions contributed to the correction of maladaptive behavior, reducing self-stigmatization, there was a positive effect on compliance with medical recommendations [34,35].

Conclusion

Approaches to improving compliance should be expanded and ideally involve not only the development of pharmacotherapy strategies, the sphere of behavioral stereotypes, patterns of emotional response and the patient's cognitive functions. It seems to be quite feasible organization of work with the patient's micro-social environment. However, all this is impossible without determining the priority areas for the correction of compliance for each patient, taking into account the individual characteristics of his personality, family relations and a number of other factors. We should not forget about the principle of continuity in the treatment of the mentally ill between hospitals and neuropsychiatric dispensaries. Methods of prediction and correction of compliance should be simplified, becoming available in clinical practice, since many experimental methods today are too laborious, expensive and require the daily presence of the patient and, therefore, they do not have practical value.

Thus, increasing patient compliance is one of the important tasks of modern psychiatry, the relevance of which is increasing due to the current trend of shifting the main means of psychiatric care to the outpatient sector. Measures aimed at improving compliance will not only improve the patient's remission quality, thereby improving the quality of life, but also reduce the number of hospitalizations, which will also reduce the burden on psychiatric hospitals and, thereby, reduce the costs of the health care system.

Reference list

1 Neznanov N.G., V.D. Vid. The problem of compliance in clinical psychiatry. Psychiatry and Psychopharmacology. 2004;6(11):159-162.

2 Velligan D, Mintz J, Maples N, et al. A randomized trial comparing in person and electronic interventions for improving adherence to oral medications in schizophrenia. Schizophr Bull. 2013;39:999–1007 doi: 10.1093/schbul/sbs116

3 Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. Am J Psychiatry. 2004;161(4):692–699 doi: 10.1176/appi.ajp.161.4.692

4 Lutova N. B., Compliance structure in patients with endogenous mental disorders. Author's abstract. The St. Petersburg Bekhterev Psychoneurological Research Institute; 2013. – 375

5 San L, Bernardo M, Gómez A, Martinez P, González B, Peña M. Socio-demographic, clinical and treatment characteristics of relapsing schizophrenic patients. Nord J Psychiatry. 2013;67(1):22–29 doi: 10.3109/08039488.2012.667150

6 Becker MA, Young MS, Ochshorn E, Diamond RJ. The relationship of antipsychotic medication class and adherence with treatment outcomes and costs for Florida Medicaid beneficiaries with schizophrenia. Adm Policy Ment Health. 2007;34(3):307–314. doi:10.1007/s10488-006-0108-5

7 Hudson TJ, Owen RR, Thrush CR, Armitage TL, Thapa P. Guideline implementation and patient-tailoring strategies to improve medication adherence for schizophrenia. J Clin Psychiatry. 2008;69(1):74–80. doi: 10.4088/jcp.v69n0110

8 Bugrova E.I. Non-compliance with the outpatient psychopharmacotherapy of schizophrenic patients: social and economic aspects, 2007. - 151 c.

9 Waddell L, Taylor M. Attitudes of patients and mental health staff to antipsychotic long-acting injections: systematic review. Br J Psychiatry Suppl. 2009;52:S43–S50. doi: 10.1192/bjp.195.52.s43

10 Patel MX, Haddad PM, Chaudhry IB, McLoughlin S, Husain N, David AS. Psychiatrists' use, knowledge and attitudes to first- and second-generation antipsychotic long-acting injections: comparisons over 5 years. J Psychopharmacol. 2009 24 1473–1482. Doi: 10.1177/0269881109104882

11 Mosolov S.N. The present stage of development of psychopharmacotherapy. Russian Medical Journal.2002;10. (12/13). 45-49.

12 Karow A, Reimer J, König HH, et al. Cost-effectiveness of 12-month therapeutic assertive community treatment as part of integrated care versus standard care in patients with schizophrenia treated with quetiapine immediate release (ACCESS trial) J Clin Psychiatry. 2012;73(3):e402–e408. Doi: 10.4088/jcp.11m06875

13 Emsley R, Chiliza B, Asmal L, Mashile M, Fusar-Poli P. Long-acting injectable antipsychotics in early psychosis: a literature review. Early Interv Psychiatry. 2013;7:247–254 doi: 10.1111/eip.12027

14 Jaeger M, Rossler W. Attitudes towards long-acting depot antipsychotics: a survey of patients, relatives and psychiatrists. Psychiatry Res. 2010;175:58–62 doi: 10.1016/j.psychres.2008.11.003

15 Danilov D.S. Therapy of schizophrenia. 2010. - 276

16 Kotzè AM, van Delft WF, Roos JL. Continuity of care of outpatients with schizophrenia in Pretoria. S Afr J Psychiatr. 2010;16(3):80–83 doi: 10.4102/sajpsychiatry.v16i3.272

17 Irzhevskaya V.P. - Violations of the awareness of mental illness in patients with schizophrenia. Moscow State University M. V. Lomonosov; 2009. - 212 pages

18 Valenstein M, McCarthy JF, Ganoczy D, et al. Assertive community treatment in veterans affairs settings: impact on adherence to antipsychotic medication. Psychiatr Serv. 2013;64(5):445–451. 451.e1. Doi: 10.1176/appi.ps.201100543

19 E. F. Pinto, S. Sahoo, D. Deshmukh, N. Vadlamani, I. Dhingra, S. Karia, Treatment compliance and noncompliance in psychosis: Methodological issues, Indian J Psychiatry. 2017 Jul-Sep; 59(3): 401–402 doi: 10.4103/psychiatry.indianjpsychiatry_343_17

20 Rodrigo C, Welgama S, Wijeratne T, Weligepola R, Rajapakse S, Jayananda G. A prospective cohort study on the role of nonspecialist staff in preventing relapses and improving clinic attendance of patients with schizophrenia. Indian J Psychiatry. 2013;55(1):74–76 doi: 10.4103/0019-5545.105518

21 Chen J, Ascher-Svanum H, Nyhuis AW, et al. Reasons for continuing or discontinuing olanzapine in the treatment of schizophrenia from the perspectives of patients and clinicians. Patient Prefer Adherence. 2011;5:547–554 doi: 10.2147/ppa.s23255

22 McHugo GJ, Bebout RR, Harris M, et al. A randomized controlled trial of integrated versus parallel housing services for homeless adults with severe mental illness. Schizophr Bull. 2004;30(4):969–982 doi: 10.1093/oxfordjournals.schbul.a007146

23 C. De las Cuevas, J. de Leon, W. Peñate, and M. Betancort Factors influencing adherence to psychopharmacological medications in psychiatric patients: a structural equation modeling approach. Patient Preference and Adherence. 2017; 11: 681–690. Doi: 10.2147/ppa.s133513

24 Peuskens J, Olivares JM, Pecenak J, et al. Treatment retention with risperidone long-acting injection: 24-month results from the Electronic Schizophrenia Treatment Adherence Registry (e-STAR) in six countries. Curr Med Res Opin. 2009;26:501–509. Doi: 10.1185/03007990903488670

25 Vervloet M, Linn AJ, van Weert JC, de Bakker DH, Bouvy

ML, van Dijk L. The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature. J Am Med Inform Assoc. 2012;19:696–704 doi: 10.1136/amiajnl-2011-000748

26 Montes JM, Medina E, Gomez-Beneyto M, Maurino J. A short message service (SMS)-based strategy for enhancing adherence to antipsychotic medication in schizophrenia. Psychiatry Res. 2012;200:89–95. Doi: 10.1016/j.psychres.2012.07.034

27 McCann TV, Clark E, Lu S. Subjective side effects of antipsychotics and medication adherence in people with schizophrenia. J Adv Nurs. 2009;65(3):534–543. Doi: 10.1111/j.1365-2648.2008.04906.x

28 Jaeger S, Pfiffner C, Weiser P, Kilian R, Becker T, Längle G, et al. Adherence styles of schizophrenia patients identified by a latent class analysis of the Medication Adherence Rating Scale (MARS): a six-month follow-up study. Psychiatry Res. 2012;200:83–8 doi: 10.1016/j.psychres.2012.03.033

29 Manuel JI, Covell NH, Jackson CT, Essock SM. Does assertive community treatment increase medication adherence for people with co-occurring psychotic and substance use disorders? J Am Psychiatr Nurses Assoc. 2011;17(1):51–56. doi: 10.1177/1078390310395586

30 Aagaard J, Müller-Nielsen K. Clinical outcome of assertive community treatment (ACT) in a rural area in Denmark: a case-control study with a 2-year follow-up. Nord J Psychiatry. 2011;65(5):299–305. doi: 10.3109/08039488.2010.544405

31 Rabinovitch M, Cassidy C, Schmitz N, Joober R, Malla A. The influence of perceived social support on medication adherence in first-episode psychosis. Can J Psychiatry. 2013;58(1):59–65. doi: 10.1177/070674371305800111

32 Wilk JE, West JC, Marcus SC, Countis L, Regier DA, Olfson M. Family contact and the management of medication non-adherence in schizophrenia. Community Ment Health J. 2008;44(5):377–380. doi: 10.1007/s10597-008-9139-6

33 R. Kemp, A. David, P. Hayward. Modern Psychiatry Overview. 2000.5.91-101.

34 Babin S.M., Shlafer A.M., Sergeeva N.A., Compliance therapy for patients with schizophrenia [electronic resource]. Medical psychology in Russia. 2011. N 2.

35 M. Krzystanek, K. Krysta, K. Skałacka Treatment Compliance in the Long-Term Paranoid Schizophrenia Telemedicine Study. J Technol Behav Sci. 2017; 2(2): 84–87. doi: 10.1007/s41347-017-0016-4

Corresponding author
Igor V. Belokrylov
beliv60@yandex.ru

No conflict of interest

Credits

The problem of compliance in psychiatry

Belokrylov Igor Vladlenovich * -PhD, Head of chair, Peoples' Friendship University of Russia, Medical Institute, Department of Psychiatry and Medical Psychology. Miklukho-Maklaya str., 6, Moscow, Russia, 117198, Tel: 8-901-517-30-63

Sokolov Vladimir Pavlovich - postgraduate, Peoples' Friendship University of Russia, Medical Institute, Department of Psychiatry and Medical Psychology. Miklukho-Maklaya str., 6, Moscow, Russia, 117198, Tel: 8-964-530-65-73

Department of Psychiatry and Medical Psychology, Peoples' Friendship University of Russia. Miklukho-Maklaya str., 6, Moscow, Russia, 117198

Doi 10.26269/eyg2-vs37

Current opportunities of emergency and urgent interventional care in vascular posttraumatic damage

V.V. Boiarincev, N.V. Zakarian, A.A. Shelesko, A.S. Pankov, A.G. Davtian, E.B. Molohoev
Clinical Hospital № 1 of Department of Presidential Affairs. Moscow, Russia

Abstract

Trauma is one of the leading causes of mortality. There is a need for effective and efficient delivery of care that can improve survival and reduce morbidity as much as possible. Since the development of angiography and transcatheter techniques, interventional radiology has played an important role in the management of trauma patients. The ability to treat life-threatening hemorrhage with transcatheter embolization has spared countless patients the morbidity of surgery. As the applications of transcatheter therapy broaden to include embolization of unstable patients with solid organ injuries and endovascular repair of major arterial injuries, the interventional radiologist must be increasingly prepared to provide prompt, efficient, and high-quality service.

Key words: trauma, interventional radiology, transcatheter embolization, stent-graft.

Trauma is the third overall leading cause of mortality across all ages. It remains the leading cause of death among 1 to 44 years old causing 193,000 deaths annually in USA. The first description of the use of transcatheter embolization of the internal iliac artery to control hemorrhage associated with pelvic fractures was published in 1972.1 Since that time, the role of interventional radiologists in trauma has evolved from that of making the initial diagnosis of vascular and solid organ injuries to temporizing or definitive treatment. Interventional radiologists are ideally qualified to play an important role in the management of trauma patients. With recent advances in endovascular techniques, there is an increasing role for it in the management of traumatic hemorrhage. Equally important, treatment of trauma patients requires efficient use of resources as well as cooperation and communication among a multidisciplinary team. Patients need to be rapidly and accurately assessed to determine the nature of their injuries with treatments prioritized by injury severity. Angiography provides quick imaging, accurate diagnosis, early procedural triaging, and potentially shortens the time from diagnosis to intervention.

CATHETER ANGIOGRAPHY

Indications for emergency catheter angiography in the trauma patient include clinical signs or symptoms of hemorrhage or CT evidence of ongoing hemorrhage or vascular injury. In the selected trauma patient with suspected vascular injury or hemorrhage, diagnostic catheter angiography usually is performed. Catheter angiography may be performed as a screening procedure or to plan definitive transcatheter or surgical therapy. It is used as follows:

- A large-field nonselective study, such as an abdominal aortogram, is obtained first. Angiography may detect bleeding and may help in planning further selective studies;
- Selective studies are performed to detect more subtle hemorrhage and vascular injuries and to direct further treatment;
- Angiography should be performed as quickly as possible for the immediate diagnosis of bleeding and subsequent embolization or stenting of the area of vascular damage.

INTERVENTIONAL TREATMENT MODALITIES

The following interventional treatment methods are commonly utilized in the trauma setting:

- **BALLOON OCCLUSION:** Inflation of an angioplasty balloon proximal to a major arterial injury may temporarily stop or reduce life-threatening hemorrhage and thereby stabilize the patient while definitive surgical or endovascular repair is being arranged;
- **TRANSCATHETER EMBOLIZATION:** Embolization is an intentional occlusion of a vessel to arrest blood flow by deposition of embolic materials directly into the vessel via an angiographic catheter. Transcatheter embolization can stop arterial hemorrhage, thus improving unstable hemodynamics and often avoiding the need for surgery. The primary goal of embolization is to control the hemorrhage at its source intravascularly. The secondary goal is to prevent embolic material traveling to non-targeted organ tissue, thereby preventing organ dysfunction and associated sequelae. Prompt, effective, and safe transcatheter embolization requires skill and knowledge of the available equipment, arterial anatomy, role of collateral arterial flow, and risks. A variety of catheters, including coaxial microcatheters, are available for selective catheterization to virtually all parts of the arterial cir-

culation. Embolic agents vary in their permanency and the anticipated level of arterial occlusion. The choice of embolic agent will vary based on the site and nature of the injury, the desire to preserve collateral flow, and operator preference. Gelfoam, microparticles and coils are some of the most commonly selected embolic agents in trauma. Transcatheter embolization of active hemorrhage or vascular injury often is considered preferable to surgical treatment. Transcatheter embolization is the mainstay of modern interventional trauma radiology.

- **STENTS:** Stent-grafts or covered stents provide a means of salvaging injured or hemorrhaging arteries and increase the options for transcatheter treatment. Stent-grafts are increasingly being applied to the treatment of large vessel injuries and may enable one to avoid complex surgical vascular repairs in areas with trauma-related anatomic distortion and in patients who may be unstable. Stent grafts have been used successfully in the treatment of arterial rupture or pseudoaneurysm in suitable vessels. Bare stents have been used successfully in the treatment of intimal dissection.

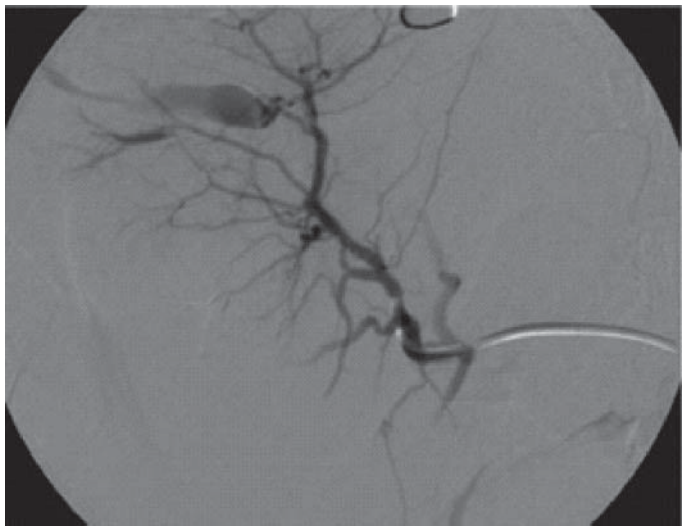
SOLID VISCERAL INJURIES

The spleen is the most commonly injured solid abdominal organ, closely followed by the liver, with injuries occurring as the result of blunt or penetrating trauma. Less frequently the kidney, mesentery, adrenal gland, small bowel, or pancreas is injured.2 In the past, surgery was the only treatment for control of hemorrhage. However, transcatheter embolization quickly earned a role in the nonoperative management of these injuries, particularly where organ preservation was important (Fig. 1).

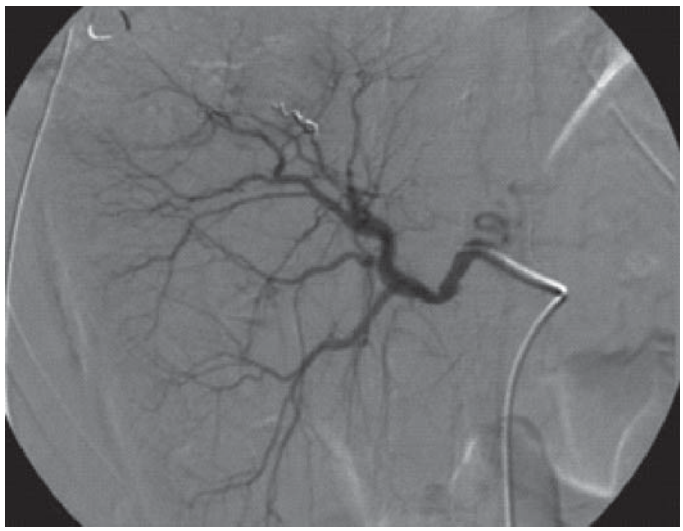
Imaging plays a large role in the evaluation of trauma patients. Computed tomography (CT) is the best imaging study for evaluation of stable trauma patients. Its sensitivity for injury approaches 100%. Arterial extravasation is identified as a focus or area of high contrast attenuation that does not conform to a normal vascular structure, surrounded by the high-attenuation fluid of a hematoma or is situated within an injured solid organ. This extravasation may be contained, as in the case of a pseudoaneurysm, or uncontained with free spill into the peritoneum. CT-angiography can also be used to evaluate large-vessel integrity with diagnosis of arterial occlusions, transections, dissections, intimal tears, and more.

SPLEEN

Patients with hemodynamic instability and evidence of splenic trauma typically undergo immediate surgery. Hemodynamically stable patients with splenic injury are triaged to nonoperative management with observation or transcatheter embolization. The decision as to who should undergo angiography has changed over time. Early reports advocated mandatory angiography for all patients with imaging evidence of splenic injury who did not undergo immediate surgery.3,4 Unfortunately, many patients did not prove to have arterial injuries at angiography and did not require transcatheter embolization. Subsequently, clinical and imaging parameters were successfully used to stratify patients into those who required angiography and those who could be observed. This division avoided angiography in a majority (74%) of patients.5 CT is the imaging modality of choice to make the diagnosis of splenic injury, and it may help in grading the degree of injury. Currently, the accepted indication for angiography is the presence of active extravasation or pseudoaneurysm formation at CT.6,7 This ''contrast blush'' is strongly correlated with failure of observa-

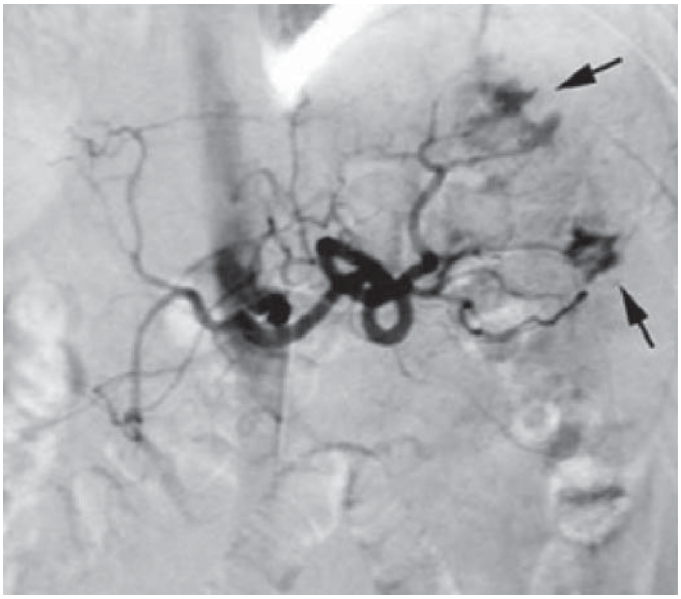


A

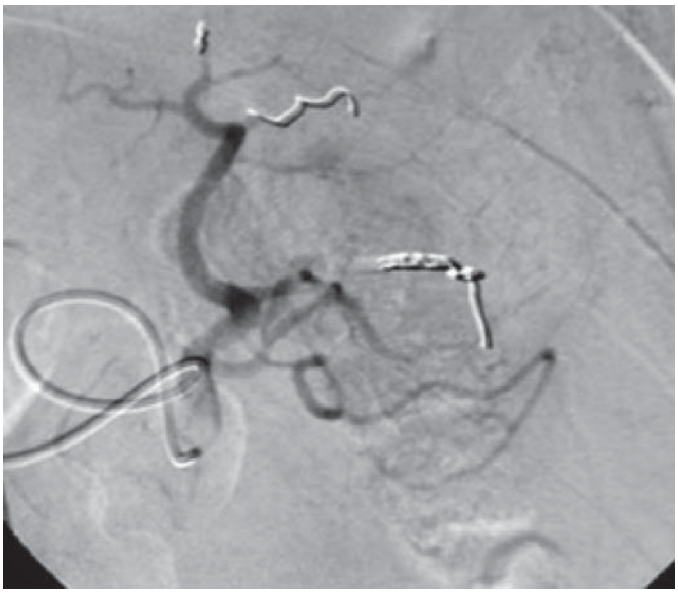


B

Figure 1. Angiography confirms the extravasation in the right hepatic lobe (A), which was successfully treated with transcatheter embolization using coils super selectively deployed in the bleeding vessel with preservation of surrounding branches (B)



A



B

Figure 2. Celiac angiogram showing 3 foci of extravasation in spleen (A), after super selective embolization splenic angiogram demonstrating microcoils in good position and no evidence of further extravasation (B).

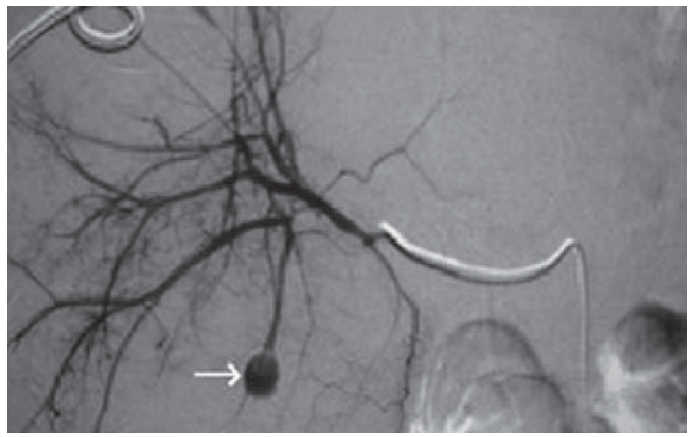
tion as nonoperative management.8,9 Stable patients with splenic injuries that do not demonstrate one of these findings can be observed. Most will recover uneventfully, though some will experience delayed hemorrhage requiring intervention.

Two methods are available for splenic transcatheter embolization, proximal and distal embolization, both with proven success. Proximal coil embolization just distal to the dorsal pancreatic artery and proximal to the pancreatic magna artery to reduces pulse pressure to the spleen, promoting native hemostasis, but preserves flow to the spleen through collaterals. Coils should be just larger than the vessel diameter to avoid distal embolization or protrusion into the celiac artery.

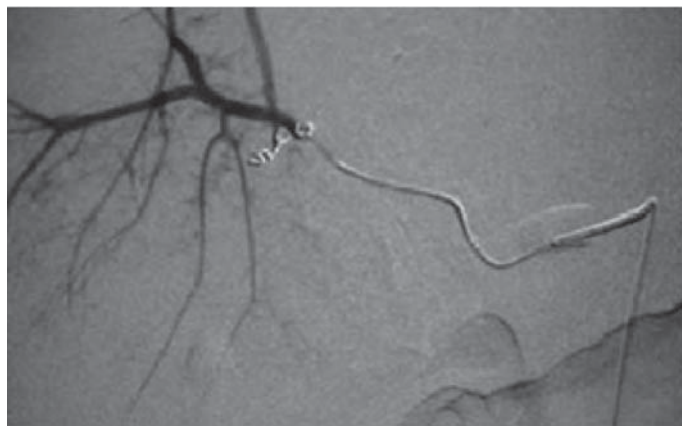
Distal embolization is typically performed using gelfoam or microparticles distributed by flow. A variant of this is super selective embolization of a single injured vessel, which can be performed using a microcatheter with particles or coils but requires increased time and skill (Fig. 2). Combinations of proximal and distal transcatheter embolization may be useful in some cases. Not surprisingly, postprocedural CT has demonstrated a higher rate and larger size of splenic infarcts following distal embolization as compared with proximal embolization.10,11,12 Thus, proximal transcatheter embolization is recommended for organ preservation with distal transcatheter embolization reserved for refractory hemodynamic instability or control of extra parenchymal extravasation.

LIVER

Hepatic trauma can result in injuries to the hepatic arteries, portal veins or hepatic veins. The mortality rate of surgery for blunt hepatic trauma has been reported to be 33% or greater.13 Therefore, nonoperative management is the treatment of choice for stable patients and may increasingly be selected for some unstable patients as well. CT has proven useful in the



A



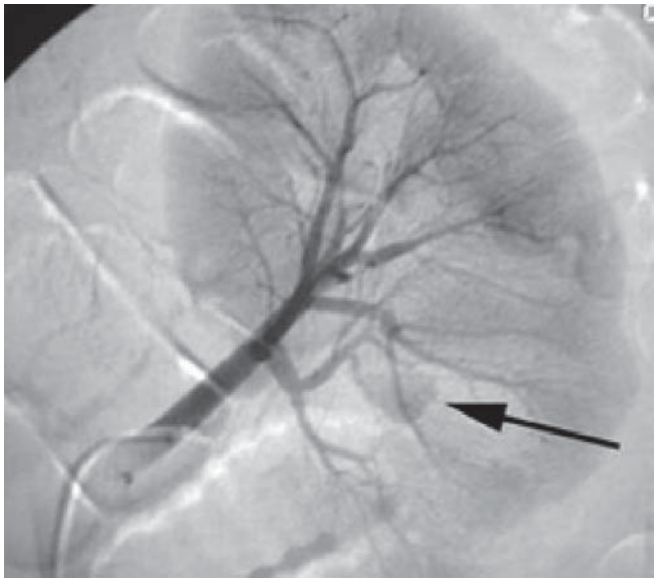
B

Figure 3. Embolization of traumatic pseudoaneurysm of the hepatic artery (arrow) (A), after selective embolization hepatic angiogram demonstrating microcoils in good position and completely occluding pseudoaneurysm of the hepatic artery (B).

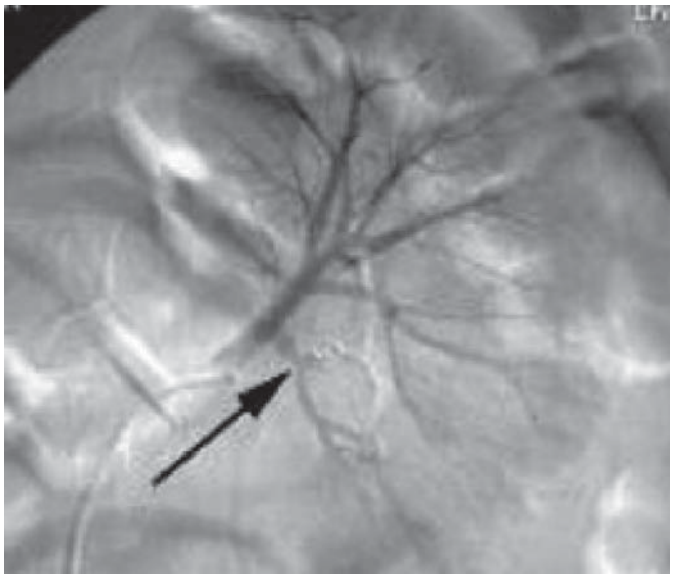
identification of patients who require angiography.14 An estimated 50 to 80% of patients with blunt hepatic trauma should be able to undergo nonoperative management with avoidance of surgery in 98.5%.15 The dual blood supply of the liver makes infarction from transcatheter embolization unlikely provided the portal vein is patent and flow is antegrade, findings that can be confirmed at angiography. In some cases, super selective catheterization and embolization can be performed to preserve uninjured tissue (Fig. 3). Less selective embolization of an entire hepatic lobe or segment may be performed using gelfoam or micro-embollic particles. This method is preferred to treat multiple sites of injury simultaneously and when prompt cessation of hemorrhage is necessary and super selective catheterization is too time-consuming.

KIDNEY

A recent series of consensus documents on genitourinary trauma highlights the evaluation and management of renal injuries.16 Similar to hepatic and splenic trauma, the indications for angiography have varied with time but have a basis in CT imaging. Generally, patients with severe injuries or instability are taken to surgery, but one recent report advocated mandatory angiography of high-grade injuries whenever the clinical condition allowed it, even in the setting of hypotension.17 Embolization should be performed as selectively as possible to preserve uninjured renal parenchyma. Super selective embolization preserves renal function, sometimes better than surgery.18 Both gelfoam and coils are appropriate, though gelfoam may allow for recanalization and tissue preservation. With increasing experience, the role of interventional treatment may expand to include stent-graft insertion for repair of large vessel injury. Transcatheter embolization of injuries to the branch arteries is successful in 84-100% of patients (Fig. 4).18



A

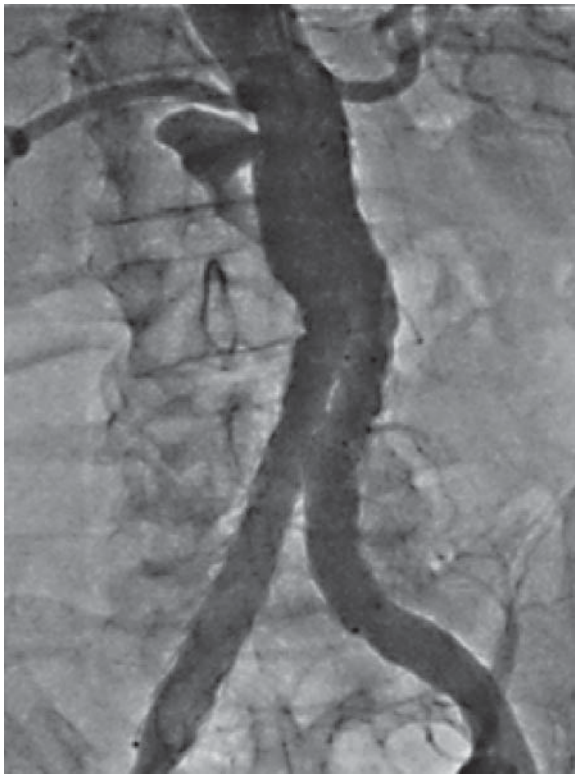


B

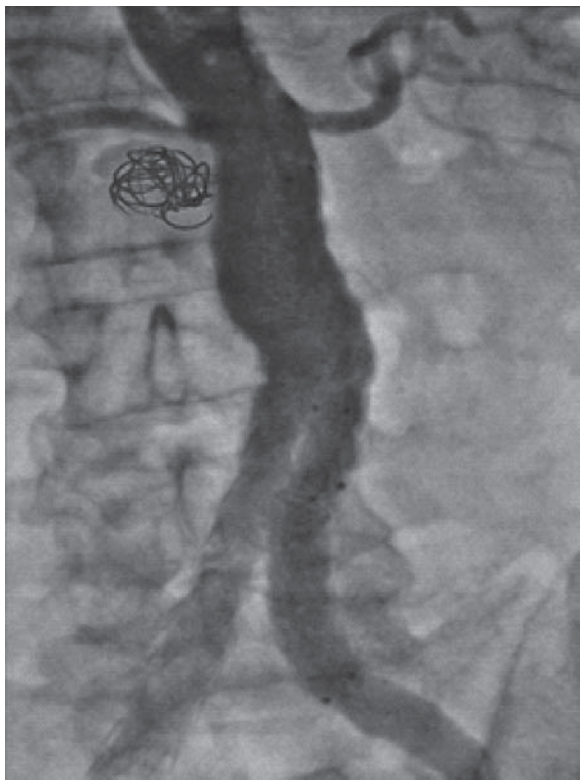
Figure 4. Left renal angiogram demonstrate a pseudoaneurysm (arrow) of an intrarenal artery branch (A), left renal angiogram shows coil embolization (arrow) completely occluding the renal artery branch previously containing the pseudoaneurysm (B).

AORTA

The aortic injury most concerning in blunt trauma is acute aortic transection, or acute traumatic aortic injury, due to its high mortality. Most patients die before transport to the hospital. Of those who reach the hospital, the overall survival rate is 70% with higher mortality associated with delays in treatment.19 Additional injuries of the aorta and its branches may occur from trauma as well, including intimal tears and dissections. Therapy is generally guided by the nature of the injury and the presence or risk of organ compromise. A high degree of suspicion is needed to diagnose acute traumatic aortic injury. Contrast-enhanced CT has proven utility in evaluation of patients with abnormal chest radiographs and patients for whom there is a high clinical suspicion. 20,21 A normal CT has a negative predictive value of 100% for acute traumatic aortic injury.22 In the past, all patients with abnormal chest CT exams underwent catheter angiography. Catheter angiography has generally been considered the gold standard for diagnosis of acute traumatic aortic injury, but CT-angiography has shown sensitivity, specificity, and accuracy similar to catheter angiography and is supplanting this procedure in many medical centers.19,22 Acute traumatic aortic injury is associated with rapid deceleration in motor vehicle collisions, falls from a height, and crush injuries.19 Most injuries involve partial or full-thickness disruptions of the aortic wall. In patients who reach the hospital alive, 90% occur at the aortic isthmus, with smaller proportions in the ascending aorta just above the aortic valve (8%)

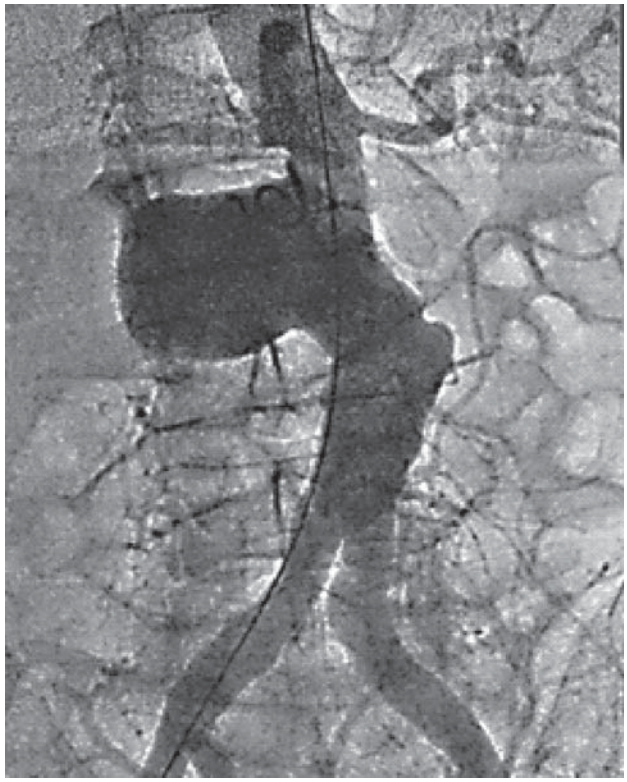


A

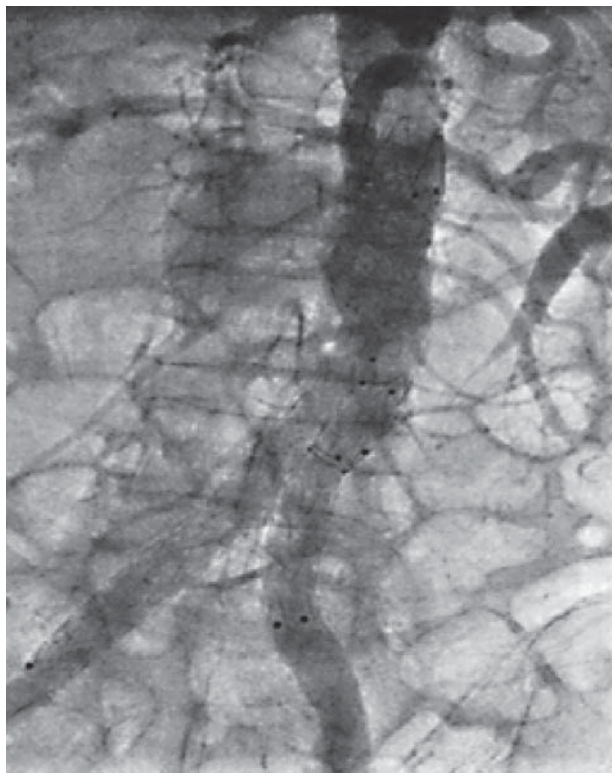


B

Figure 5. Posttraumatic pseudoaneurysm sac in stent grafted abdominal aorta (A), treated with transcatheter coil embolization (B).



A



B

Figure 6. Posttraumatic infrarenal aneurysm of abdominal aorta (A), treated with endoprosthesis aortic aneurysm using a stent graft (B).

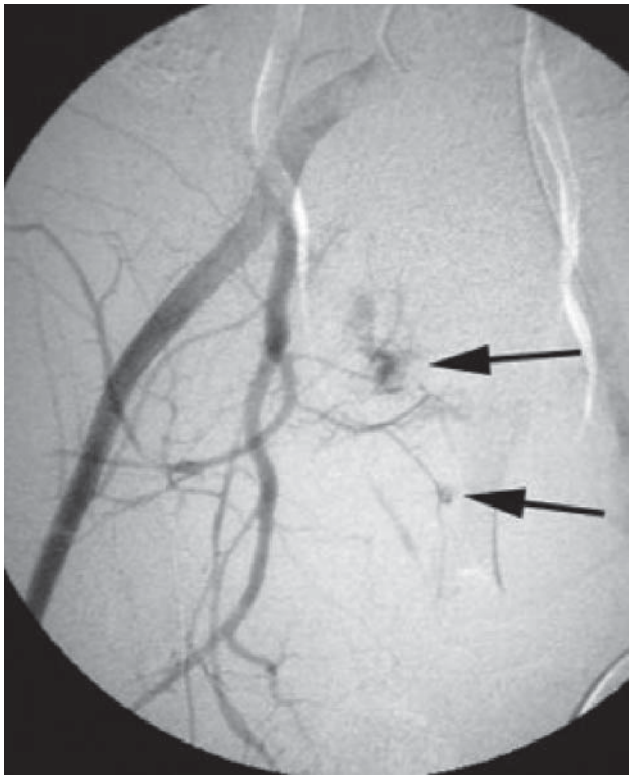
and in the descending aorta at the diaphragmatic hiatus (2%).[22]

Arteriography should include at least two different views of the aortic arch - typically a 45° left anterior oblique and an anteroposterior view. Additional views including right anterior oblique and lateral projections can be obtained as needed. Arteriographic findings include an abnormality or outpouching of the aortic contour, an intimal flap or dissection, retention of contrast in a pseudoaneurysm sac (Fig. 5). The proxi-

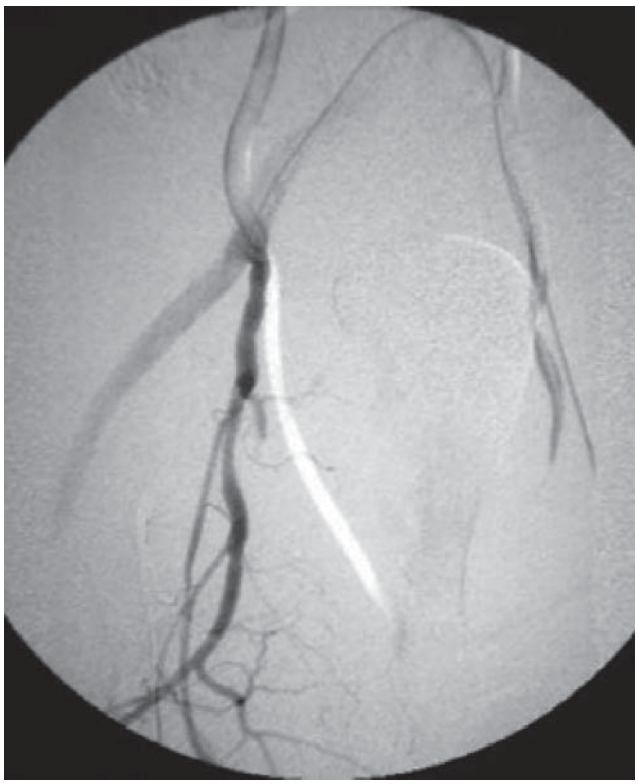
mal segments of the great vessels should be carefully assessed for associated injuries. Treatment of acute traumatic aortic injury has traditionally been operative repair, but increasingly patients are being treated with endovascular stent-grafts (Fig. 6). Emergency surgery for treatment of acute traumatic aortic injury has mortality rates of 15 to 29% with higher mortality in the elderly.[23]

PELVIS

Most patients with pelvic fractures are hemodynamically stable. A small percentage, particularly those with unstable fractures, present with hemodynamic instability. Pelvic fractures alone are associated with mortality rates of 5.6 to 15%, but the addition of hemorrhagic shock raises rates from 36 to 54%.24 Death due to hemorrhage frequently occurs in the first 24 hours, and the mortality rate rises with delays in treatment.25,26 Associated organ injuries have been found in 11 to 20.3%,24 injuries that can increase morbidity and mortality. Failure to treat or delay in treatment can result in death due to hemorrhage or abdominal compartment syndrome. Pelvic hemorrhage most commonly arises from fractured bones or disrupted pelvic veins with only 10 to 20% of severe hemorrhage from arterial injury.27 Hemodynamically unstable patients with pelvic fractures require aggressive resuscitation. Treatments for traumatic pelvic hemorrhage include external fixation of unstable fractures, transcatheter embolization, and pelvic packing. Open surgical procedures like packing are not advised due to the loss of the tamponade effect of the contained hematoma, risking large-volume, uncontrolled venous and/or arterial bleeding.28 External fixation apposes bone surfaces and reduces pelvic volume, enhancing tamponade from the enlarging hematoma. This maneuver may stop bleeding from bone surfaces and veins but is unlikely to stop arterial bleeding30 and delays transcatheter embolization. Arterial bleeding at angiography has been associated with a lack of response to initial resuscitation, the pelvic fracture pattern, the amount and location of pelvic hematoma, and active extravasation of contrast at CT.29,31 CT with contrast diagnoses and localizes arterial extravasation from pelvic trauma with a sensitivity of 60 to 90%, a specificity of 85 to 98%, and an accuracy of 87 to 98%.24,31 CT evidence of extravasation in the pelvis is an indication for transcatheter embolization. The internal pudendal artery and superior gluteal arteries are two of the most commonly injured pelvic arteries.25,27 Most arterial hemorrhage originates from branches of the internal iliac arteries. Nonselective pelvic arteriography can be useful to localize and lateralize a site of hemorrhage. Selective arteriography of the internal iliac arteries should follow. Currently accepted indications for transcatheter embolization include active extravasation, arterial branch irregularity or truncation, one or more pseudoaneurysms, and arteriovenous fistula for-



A



B

Figure 7. Right iliac angiogram demonstrating acute extravasation (arrows) from the right superior and inferior lateral sacral arteries (A), post embolization study of the right iliac artery showing occlusion of the posterior division and internal pudendal artery and no extravasation is evident (B).

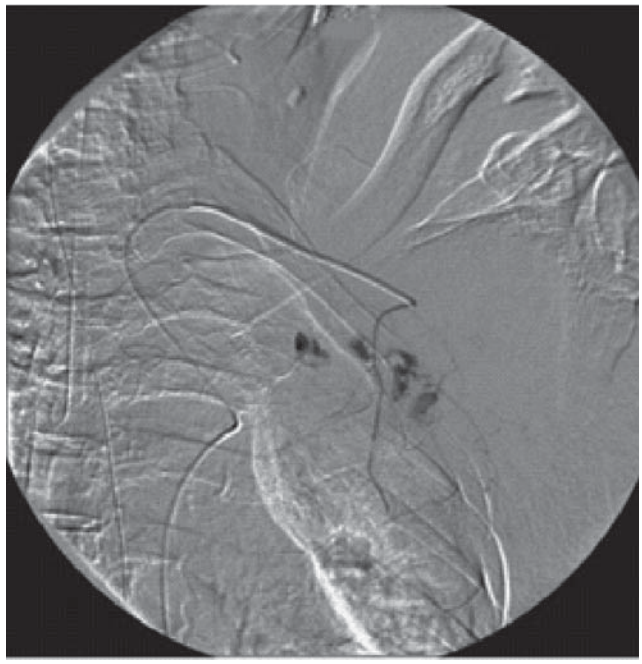
mation (Fig. 7). Transcatheter embolization of pelvic trauma that is performed early, within 3 hours of presentation, has been shown to lower the mortality rate. Overall, angiography is required in fewer than 10% of patients with pelvic trauma. When angiography is performed, extravasation is documented in approximately one half of patients; in such cases, transcatheter embolization is warranted.

The chosen embolic agent and technique should provide hemostasis while preserving normal vessels and collateral flow where possible. Gelfoam and micro-embolic particles has been the agent of choice due to its temporary nature. Coils, however, may be appropriate for single arterial abnormalities and for distal to proximal embolization across the neck of a large vessel pseudoaneurysm. Distal gelfoam embolization from a proximal catheter position may be necessary if the patient is unstable, selective catheterization is overly time-consuming, or there are multiple arterial injuries in the supplied region. Proximal embolization with coils to decreased pulse pressure to a site of bleeding is not generally successful due to the robust pelvic collateral network. It is important to evaluate the contralateral internal iliac artery to exclude continued hemorrhage from collaterals or additional sites of bleeding. Success rates for transcatheter embolization range from 85 to 100% with mortality rates of 17.6 to 47% despite successful embolization.24 Lower mortality rates have been associated with early embolization.25 Higher mortality has been seen in older patients and patients with greater hemodynamic compromise and concomitant injuries.25,29

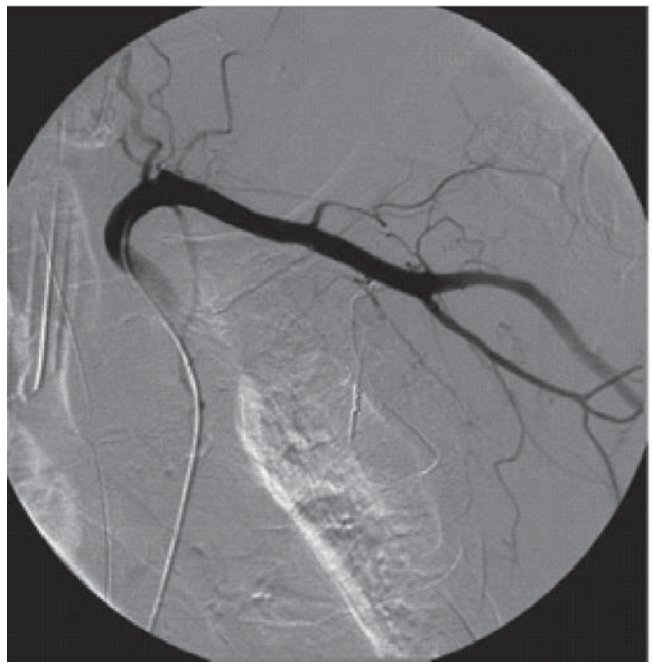
EXTREMITIES

The extremities are frequently injured in trauma, particularly penetrating trauma from gunshot and stab wounds, but arterial injuries can also occur in blunt trauma, typically due to crush injuries, tissue disruption, joint dislocation and laceration from broken bones or penetration by external objects. Currently, most patients with hard signs of vascular injury or evidence of compartment syndrome undergo immediate surgery. Delays in treatment of major arterial injuries have been associated with the need for amputation. Early recognition with vascular repair has improved limb salvage.32,33 Catheter angiography is indicated in cases of known or suspected peripheral vascular injury when the location of the injury is not certain, when multiple injury sites may be present, when the diagnosis requires confirmation, or when transcatheter treatment may be the therapy of choice. Angiography should begin with a nonselective injection of the thoracic arch for upper extremity evaluation and the abdominal aorta or ipsilateral iliac system for lower extremity evaluation. A complete evaluation will often require selective and possibly sub-selective catheterization of the affected extremity. Imaging at the injury site should be performed in at least two projections as subtle injuries and intimal tears may be visible only on one view. Major angiographic findings include active extravasation, large pseudoaneurysms, and arterial occlusion or transection (Fig. 8). Minor angiographic findings include vessel narrowing or displacement by hematoma, spasm, obstruction of minor noncritical branches, small pseudoaneurysms or arteriovenous fistulas.

Transcatheter treatments include balloon occlusion, embolization, and endovascular repair with

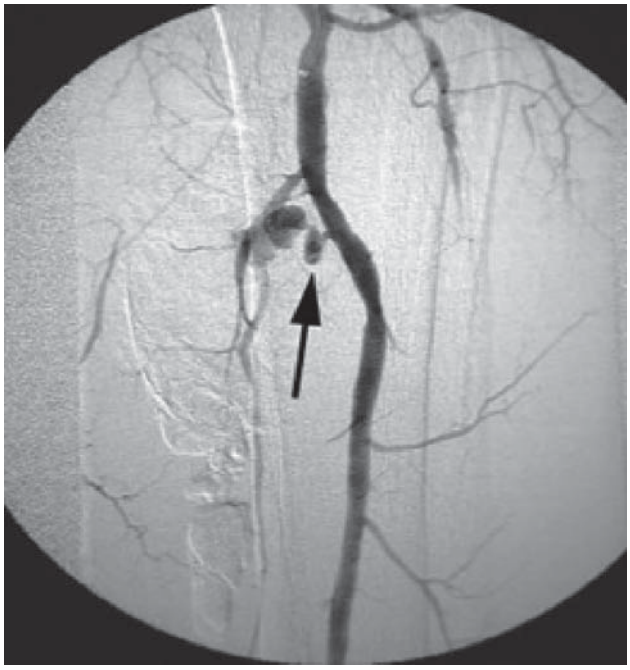


A

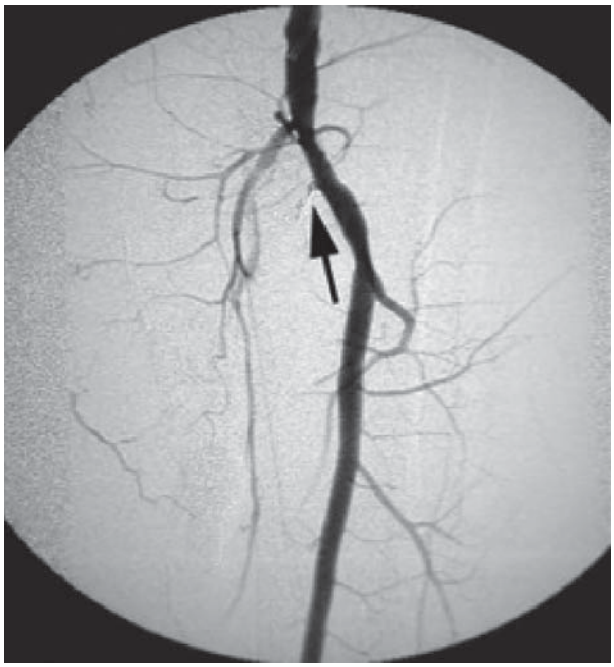


B

Figure 8. Active extravasation of the left brachial artery (A), treated with transcatheter coil embolization (B).



A



B

Figure 9. Left lower extremity angiogram shows extravasation (arrow) from the proximal part of the peroneal artery (A), after embolization of the left peroneal artery with detachable microcoil (arrow) no further extravasation is identified (B).

stent-grafting. Injuries of the aorta or large proximal extremity vessels like the subclavian artery or superficial femoral artery are particularly life-threatening and balloon occlusion can be particularly helpful. Coils are often the best agent for embolization of small vessel injuries (Fig. 9). An appreciation of the collateral circulation to the distal extremity is necessary to determine the safety of and method to avoid reflux of particles causing nontarget embolization. Though arterial transactions, dissections, and occlusions have traditionally been repaired surgically, there has been increasing interest in endovascular repair using stent-grafts.33 Reports are available on endovascular treatment of the aorta,23 the carotid artery,34 the subclavian artery,35 the brachial artery,34 and the iliac arteries.32 Many of the reported repairs using stent-grafts occurred when operative repair was associated with a greater than normal difficulty or there was an immediate need for cessation of hemorrhage.35 There are little data on long-term utility and safety of this treatment. The choice of stent-graft should also take into consideration the location of the injury and the potential for external compression, which could crush or deform a stent-graft. CT-angiography is increasingly useful in the evaluation of extremity arterial injury and is replacing catheter angiography in some settings.33 CT-angiography has a sensitivity of 90 to 95.1% and a specificity of 98.7 to 100% for detection of extremity arterial injury.35 Catheter angiography can typically be performed if additional information is needed.

CONCLUSION

Trauma leaders worldwide show a growing interest in using endovascular tools in trauma resuscitation, hemorrhage control and definitive injury management. Interventional radiology has much to offer in the evaluation and treatment of traumatic injuries. Current literature suggests that this role may expand in time due to desire for organ preservation and avoidance of surgery as well as due to improvements in transcatheter equipment. A solid understanding of the benefits and risks of the different transcatheter therapies is required to provide patients with the best care possible. Effective integration with surgery and emergency medicine requires adequate staffing, organized multidisciplinary evaluation and direct communication with quick response times. Customized hybrid operating rooms equipped for resuscitation, angiographic intervention, imaging capability, and surgical management of trauma patients are becoming the wave of the future for delivering expedited multidisciplinary care. Continued vigilance on the part of the trauma and surgical communities to incorporate the interventionalist into the trauma team is required. Embolization represents a safe and effective technique for rapidly achieving hemostasis. Interventionalists welcome this complimentary role in trauma care that allows for not only definitive treatment of vascular injuries but also for selection of those patients who may ultimately experience failure of conservative management. A therapeutic alliance between trauma surgeons and interventional radiologists will advance the standard of care for trauma.

REFERENCES

1. McGahan JP, Wang L, Richards JR. Focused abdominal US for trauma. Radiographics 2001; 21:S191–S199

2. Yao DC, Jeffrey RB, Mirvis SE, et al. Using contrast- enhanced helical CT to visualize arterial extravasation after blunt abdominal trauma: incidence and organ distribution. AJR Am J Roentgenol 2002; 178:17–20

3. Haan J, Scott J, Boyd-Kranis RL, Ho S, Kramer M, Scalea TM. Admission angiography for blunt splenic injury: advantages and pitfalls. J Trauma 2001; 51:1161–1165

4. Sclafani SJ, Shaftan GW, Scalea TM, et al. Nonoperative salvage of computed tomography—diagnosed splenic injuries: utilization of angiography for triage and embolization for hemostasis. J Trauma 1995; 39:818–827

5. Dent D, Alsabrook G, Erickson BA, et al. Blunt splenic injuries: high nonoperative management rate can be achieved with selective embolization. J Trauma 2004; 56:1063–1067

6. Omert LA, Salyer D, Dunham M, Porter J, Silva A, Protetch J. Implications of the "contrast blush" finding on computed tomographic scan of the spleen in trauma. J Trauma 2001;51: 272–278

7. Cox CS, Geiger JD, Liu DC, Garver K. Pediatric blunt abdominal trauma: role of computed tomography vascular blush. J Pediatr Surg 1997; 32:1196–1200

8. Schurr MJ, Fabian TC, Gavant M, et al. Management of blunt splenic trauma: computed tomographic contrast blush predicts failure of nonoperative management. J Trauma 1995; 39:507–513

9. Bessoud B, Denys A, Calmes JM, et al. Non-operative management of traumatic splenic injuries: is there a role for proximal splenic artery embolization? AJR Am J Roentgenol 2006; 186:779–785

10. Haan JM, Bochicchio GV, Kramer N, Scalea TM. Non- operative management of blunt splenic injury: a 5-year experience. J Trauma 2005; 58:492–498

11. Killeen KL, Shanmuganathan K, Boyd-Kranis R, Scalea TM, Mirvis SE. CT findings after embolization for blunt splenic trauma. J Vasc Interv Radiol 2001; 12:209–214

12. Wahl WL, Ahrns KS, Chen S, Hemmila MR, Rowe SA, Arbabi S. Blunt splenic injury: operation versus angiographic embolization. Surgery 2004; 136:891–899

13. Schwartz RA, Teitelbaum GP, Katz MD, Pentecost MJ. Effectiveness of transcatheter embolization in the control of hepatic vascular injuries. J Vasc Interv Radiol 1993; 4:359– 365

14. Poletti PA, Mirvis SE, Shanmuganathan K, Killeen KL, Coldwell D. CT criteria for management of blunt liver trauma: correlation with angiographic and surgical findings. Radiology 2000; 216:418–427

15. Pachter HL, Knudson MM, Esrig B, et al. Status of nonoperative management of blunt hepatic injuries in 1995: a multicenter experience with 404 patients. J Trauma 1996;40: 31–38

16. Santucci RA, Wessells H, Bartsch G, et al. Consensus on genitourinary trauma. Evaluation and management of renal injuries: consensus statement of the renal trauma subcommittee. BJU Int 2004; 93:937–954

17. Hagiwara A, Sakaki S, Goto H, et al. The role of interventional radiology in the management of blunt renal injury: a practical protocol. J Trauma 2001; 51:526–531

18. Richman SD, Green WM, Kroll R, Casarella WJ. Super- selective transcatheter embolization of traumatic renal hemorrhage. AJR Am J Roentgenol 1977; 128:843–844

19. Wintermark M, Wicky S, Schnyder P. Imaging of acute traumatic injuries of the thoracic aorta. Eur Radiol 2002;12: 431–442

20. Richardson P, Mirvis SE, Scorpio R, Dunham CM. Valueof CT in determining the need for angiography when findings of mediastinal hemorrhage on chest radiographs are equivocal. AJR Am J Roentgenol 1991; 156:273–279

21. Cohen AM, Crass JR. Traumatic lacerations of the aorta and great vessels with a normal mediastinum at radiography. J Vasc Interv Radiol 1992;3:541–544

22. Alkadhi H, Wildermuth S, Desbiolles L, et al. Vascular emergencies of the thorax after blunt and iatrogenic trauma: multidetector row CT and three-dimensional imaging. Radiographics 2004; 24:1239–1255

23. Homma H, Yukioka T, Ishimaru S, et al. Two-year follow-up after multiple injuries treated with endovascular stent-grafting of aorta and transcatheter arterial embolization of spleen: minimal invasive surgery for an elderly patient. J Trauma 2002;52: 382–386

24. Yoon W, Kim JK, Jeong YY, Seo JJ, Park JG, Kang HK. Pelvic arterial hemorrhage in patients with pelvic fractures: detection with contrast-enhanced CT. Radiographics 2004; 24:1591–1606.

25. Agolini SF, Shah K, Jaffe J, Newcomb J, Rhodes M, Reed JF. Arterial embolization is a rapid and effective technique for controlling pelvic fracture hemorrhage. J Trauma 1997; 43:395–399

26. Eastridge BJ, Starr A, Minei JP, O'Keefe GE. The importance of fracture pattern in guiding therapeutic decision-making in patients with hemorrhage shock and pelvic ring disruptions. J Trauma 2002; 53:446–451

27. Hak DJ. The role of pelvic angiography in evaluation and management of pelvic trauma. Orthop Clin North Am 2004; 35:439–443

28. Ghanayem AJ, Wilber JH, Lieberman JM, Motta AO. The effect of laparotomy and external fixator stabilization on pelvic volume in an unstable pelvic injury. J Trauma 1995; 38: 396–400

29. Hagiwara A, Minakawa K, Fukushima H, Murata A, Masuda H, Shimazaki S. Predictors of death in patients with life-threatening pelvic hemorrhage after successful transcatheter arterial embolization. J Trauma 2003; 55: 696–703

30. Grimm MR, Vrahas MS, Thomas KA. Pressure-volume characteristics of the intact and disrupted pelvic retroperitoneum. J Trauma 1998; 44:454–459

31. Miller PR, Moore PS, Mansell E, Meredith JW, Chang MC. External fixation or arteriogram in bleeding pelvic fracture: initial therapy guided by markers of arterial hemorrhage. J Trauma 2003; 54:437–443

32. Lyden SP, Srivastava SD, Waldman DL, Green RM. Common iliac artery dissection after blunt trauma: case report of endovascular repair and literature review. J Trauma 2001;50: 339–342

33. Rieger M, Mallouhi A, Tauscher T, Lutz M, Jaschke WR. Traumatic arterial injuries of the extremities: initial evaluation with MDCT angiography. AJR Am J Roentgenol 2006; 186:656–664

34. Miller-Thomas MM, West OC, Cohen AM. Diagnosing traumatic arterial injury in the extremities with CT angiography: pearls and pitfalls. Radiographics 2005;25: S133–S142

35. Conrad MF, Patton JH, Parikshak M, Kralovich KA. Evaluation of vascular injury in penetrating extremity trauma: angiographers stay home. Am Surg 2002; 68:269–274

Corresponding author
Zakarian Narek
narekz@yahoo.com

No conflict of interest

Doi 10.26269/p9ay-zq75

Current issues of acne treatment

L.S. Kruglova, N.V. Gryazeva, E.M. Gescheva
Central State Medical Academy, Moscow, Russia

Abstract

Purpose of the study: to analyze isotretinoin (Verocutan®) efficacy and safety in patients with moderate-to-severe juvenile and adult acne with various administration regimens. Materials and methods. 83 patients aged 12-43 with acne of variable severity were chosen for the study. Depending on the degree of severity (clinical form of the disease) and daily isotretinoin (Verocutan®) dose, the patients were divided into 4 groups. Efficacy was evaluated based on IGA and DQoL indices; special methods included corneometry and sebumetry; safety monitoring included blood biochemistry test, pregnancy test in females of child-bearing age, and adverse events. Study results: isotretinoin (Verocutan®) in different doses decreases sebum production on average by 50% in 3 months (according to sebumetric data), which promotes the achievement of IGA 0 and quality of life increase more than in 90% patients. Conclusion: 0.5 mg/kg Verocutan® is recommended for administration in moderately severe juvenile and adult acne with treatment duration of 8-10 months (during the first month, isotretinoin 20 mg may be administered to decrease the severity of predictable side effects). 0.8-1.0 mg/kg Verocutan® is recommended for administration in severe acne; if persistent clinical effect (IGA 1) is achieved during one month, isotretinoin dose can be decreased by 10 mg (in daily equivalent) every 2-3 months. Recommended treatment duration is 12 months. Low-dose regimen is recommended for patients with excoriated acne (0.2-0.3 mg/kg during the whole treatment cycle of 6 months).

Key words: juvenile acne, adult acne, excoriated acne, isotretinoin, sebumetry, corneometry, IGA, DQoL index.

Acne is one of the most common chronic dermatological inflammatory diseases, which is detected in 85% adolescents and sometimes in adults (approximately 10% population) [1].

According to modern theories of acne development, the main pathogenetic events include inflammation, sebum hyperproduction, follicular hyperkeratosis, P. acnes colonization. The point of inflammatory process application in acne are sebaceous glands. The sebaceous gland is currently considered not only a skin derivative producing sebum, but also an important regulatory organ with endocrine functions, providing for thermostatic and barrier skin functions. Besides, the sebaceous gland indirectly affects the organization of superficial skin lipids and follicular differentiation [2]. Sebaceous glands are hormone-dependent structures. As currently known, sebocyte membrane contains several types of nuclear receptors: steroid and thyroid receptors; receptors to retinoic acid, vitamin D, peroxisome proliferation activator, liver X-receptor [3]. Sebaceous glands are mostly regulated by androgens, specifically free testosterone. But 90% testosterone circulating in blood is bound with sex-steroid binding globulin (SSBG). Only in sebocytes angrogens are metabolized into free testosterone with the help of 17β- and 3β-hydroxysteroid dehydrogenase enzymes; type I 5α-reductase converts free testosterone into dehydrotestosterone (DHT). DHT stimulates sebum production and sebocyte maturation. Thus, it is safe to conclude that increased activity of 5α-reductase enzyme, increased amount of DH-receptors, or decreased SBBG synthesis (with subsequent increase of free testosterone level in blood) lead to increased function of sebaceous glands [4]. According to observations, the majority of acne patients do not demonstrate increased total testosterone level, but testosterone conversion into DHT increases 20-30-fold [5].

The majority of authors share the view that increased sebaceous gland function and sebum hyperproduction are main pathogenetic factors of acne development [6]. As sebocytes produce free fatty acids that damage sebaceous gland walls even without P. acnes action, inflammation of sebaceous glands theoretically can be aseptic, so the value of bacterial factor in acne development is somewhat overestimated.

A large number of studies performed indicate that quality of sebum is also altered in conditions of increased sebaceous gland activity and increased sebum amount [7]. When sebum is diluted, linoleic acid concentration decreases, which shifts pH to alkaine values and enables increased epidermal permeability. As one of α-linoleic acid functions is suppression of transglutaminase enzyme that regulates keratinocyte differentiation, decreased concentration of this unsaturated fatty acid in sebum ethers leads to predominance of keratinization over desquamation, retention hyperkeratosis in the follicular ostium, and sebaceous gland obstruction [8].

Jeremy A.H., Holland D. et al. demonstrated that α-linoleic acid deficiency was associated with production of IL-1α, which is an important pro-inflammatory factor [9]. Besides, decreased linoleic acid concentration increases permeability of sebaceous & hair follicles for inflammatory factors. Thus, subclinical inflammation which may precede comedone formation should be

considered primary. Congenital immunity activation in acne is accompanied with increased expression of TLRs (toll-like receptors) located on immune competent and epithelial cells of the skin; skin CD4+ lymphocytes and macrophages are activated, with subsequent increased synthesis of cytokines (interleukin (IL)-1α, IL-6, IL-8, IL-12), which in turn cause inflammatory response; antibodies are also synthesized (delayed-type hypersensitivity pattern) [10]. These changes play an important role not only in the development of inflammatory process, but also in stimulation of sebaceous glands and comedone formation [11].

Yamamoto A. and Takenouchi K. detected increased transepidermal water loss (TEWL) and corneal layer dehydration in all patients with acne. Besides, decreased total ceramides and free sphyngosine were also detected, which confirmed impaired function and structure of the intercellular lipid membrane [12]. This means that impaired skin barrier is more likely a consequence rather than the cause of the disease, being a result of increased sebaceous gland function.

Thus, acne pathology is multifactorial, including hormonal androgen impact, along with excessive sebum production, impaired keratinization, inflammation, and stimulation of congenital immune system with several pathways, including hypercolonization with P. Acnes.

Following the modern concept of acne development, the treatment should primarily target the elimination of inflammation, follicular hyperkeratosis, sebum production regulation, and elimination of P. Acnes. In 2018, the following Practical Guidelines for clinicians were published regarding acne treatment: International Consensus of the Global Alliance for Acne Treatment Result Improvement [13]. These recommendations contain the most up-to-date information on patient management. One of the main provisions in these guidelines regards the limited use of systemic and topical antibiotics due to the increasing antibiotic resistance issue [14]. According to recommendations, oral isotretinoin is the first-line drug for severe acne (cystic and conglobate acne). The experience confirms that isotretinoin can also be administered in severe papulopustular acne and in those cases where antibiotic and topical therapy is ineffective.

Issues of dose cumulation and systemic retinoid treatment duration are still being discussed. The majority of authors recommend treatment for at least 4-6 months, with achievement of complete acne resolution, though achievement of the cumulative dose (120-150 mg/kg) does not always correlate with the absence of relapses. At the same time, in patients with moderately severe and severe acne, long-term administration of daily doses less than 0.5-1.0 mg/kg can provide reliable results, as well as the use of the first-line drug without previous failed topical or systemic antibiotic therapy [15-17].

Thus, the current drug of choice for systemic acne treatment is isotretinoin, which has proven its efficacy and safety. High treatment cycle cost is considered one of the disadvantages of systemic isotretinoin. It is important to note that pharmacoeconomy has a significant impact on the treatment compliance of patients. High drug cost, especially in long-term treatment, negatively affects compliance - cases of therapy interruption or discontinuation are not so rare. In 2015, a new Russian isotretinoin drug - Verocutan® (MA No. LP-002988 dated May 07, 2015) was registered; it is manufactured in 10 and 20 mg capsules. The cost of Verocutane treatment cycle is 1.5-2 times lower than analogous drugs. An open randomized crossover study of comparative pharmacokinetics and bioequivalence was performed with drugs Vero-isotretinoin (20 mg capsules, Verofarm OJSC, Russia) and Roaccutane (20 mg capsules, R.P. Sherer, Germany). The comparison showed that pharmacokinetic parameters of those drugs did not differ significantly. According to formal criteria, drugs are bioequivalent, which allows to recommend Verocutan® for acne treatment [18].

Purpose of the study: to analyze isotretinoin (Verocutan®) efficacy and safety in patients with moderate-to-severe juvenile and adult acne with various administration regimens.

Materials and methods

83 patients with variable acne severity participated in the study. This included 49 (59.03%) females and 34 (40.97%) males. Patients' age varied from 12 to 43. Juvenile acne (moderate and severe papulopustular acne) were diagnosed in 46 (55.4%) patients, while adult acne (including excoriated acne) - in 37 (44.6%) patients. Depending on the degree of severity (clinical form of the disease) and daily isotretinoin (Verocutan®) dose, patients were divided into 4 groups (Table 1).

Patients from Groups 1 and 3 were administered low isotretinoin (Verocutan® 20 mg) doses (daily dose 0.3-0.4 mg/kg) to decrease predicted side effects that appear during the 1st month of administration to the largest extent; subsequently, patients were administered the drug in the 0.5 mg/kg dose. In Group 2, patients with severe acne were administered 0.8-1.0 mg/kg doses; when persistent clinical effect (IGA 1-0) was achieved during the final month, isotretinoin dose was decreased by 10 mg (in daily equivalent) every 2-3 months. In Group 4 (patients with excoriated acne), low-dose regimen (0.2-0.3 mg/kg) was used during the whole treatment cycle (6 months) (Table 1). All patients used basic therapy - special cosmetics, including skin cleansing and moisturizing agents.

Table 1

Clinical characteristics of patients and Verocutan® administration regimens

Group	Age (years) *M±m*	Severity/ clinical form of acne	Isotretinoin dose during the 1st month	Isotretinoin dose since the 2nd month	Duration of treatment
Group 1 n=25	15,3±1,7	Moderately severe (IGA 3) juvenile acne	20 mg	0,5 mg/kg	8 months
Group 2 n=21	16,2±0,6	Severe (IGA 4) juvenile acne	0,8-1,0 mg/kg	0,8-1,0 mg/kg	12 months
Group 3 n=20	32,1±2,8	Moderately severe (IGA 3) adult acne	20 mg	0,5 mg/kg	10 months
Group 4 n=17	34,5±1,5	Excoriated acne (IGA 2-3)	0,2 – 0,3 mg/kg	0,2 – 0,3 mg/kg	6 months

Efficacy was evaluated using clinical examination methods: IGA (Investigators Global Assessment) index, DQoL (Dermatological Quality of Life) index; and special methods: corneometry (Corneometer® CM 825, Courage & Khazaka), sebumetry (Sebumeter® SM 815, Courage & Khazaka). Parameter values in persons age-matched with study participants, but without skin lesions were taken as normal values.

The study endpoints included 1, 2, 3 months of treatment and end of treatment (6 or 12 months depending on the study group).

Safety monitoring included blood biochemistry test (before treatment, 2 and 6 months after treatment onset) - levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, triglycerides, cholesterol profile; pregnancy test in females of child-bearing age (contraceptive period duration after treatment - 1 month); adverse events (xerosis, cheilitis, mucosal dryness, retinoid dermatitis, conjunctivitis, musculoskeletal complaints).

Digital data for clinical and special investigation methods were input into Excel tables and processed using Statistica 10 software (MS Office Excel 2010). Quantitative values are presented as M ± m, where M is selected mean arithmetic, and m is standard error of mean. Qualitative values are presented as frequencies and percent. Student t-test is used to compare samples with normal distribution.

Study results

Efficacy was evaluated by inflammatory elements (papules, pustules, nodules, cysts) and retention elements (open and closed comedones). Proportion of patients with achieved IGA 0 effect in Group 1 (n=25) in 6 months was 76%, and in 8 months - 92% (Figure 1).

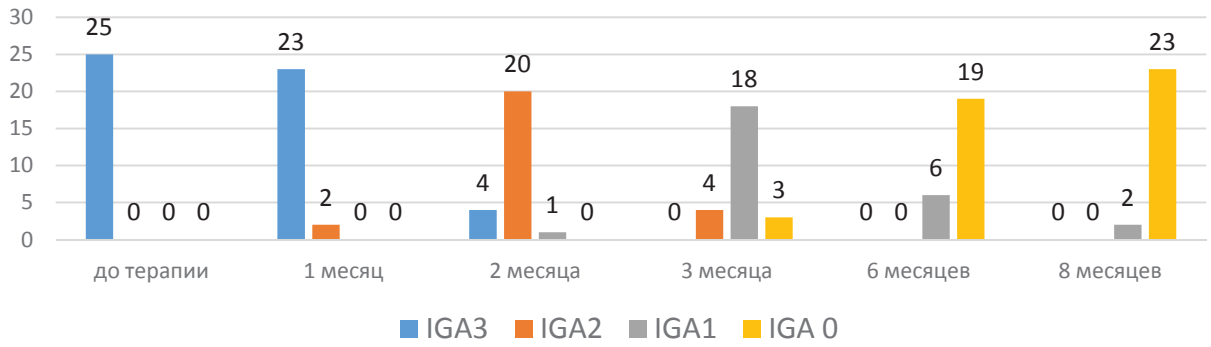


Figure 1. Details of clinical symptom changes (IGA) in Group 1 patients against the background of Verocutan® administration.

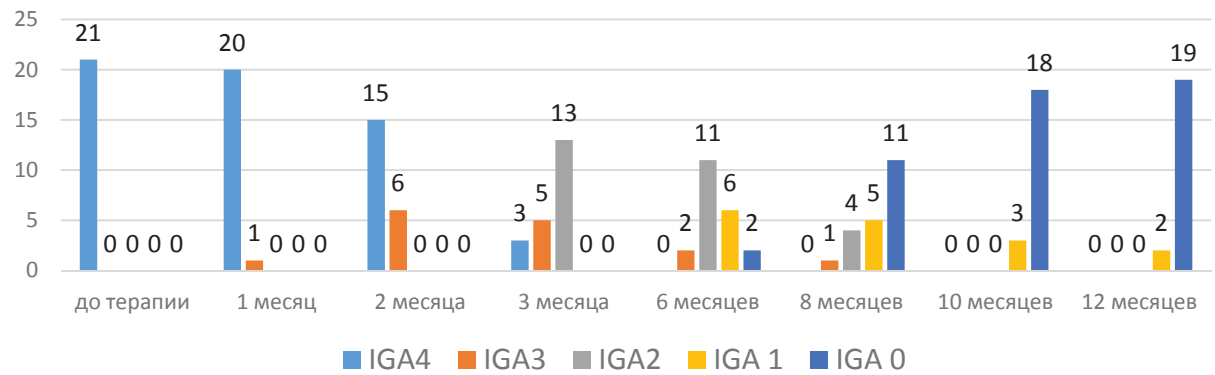


Figure 2. Details of clinical symptom changes (IGA) in Group 2 patients against the background of Verocutan® administration.

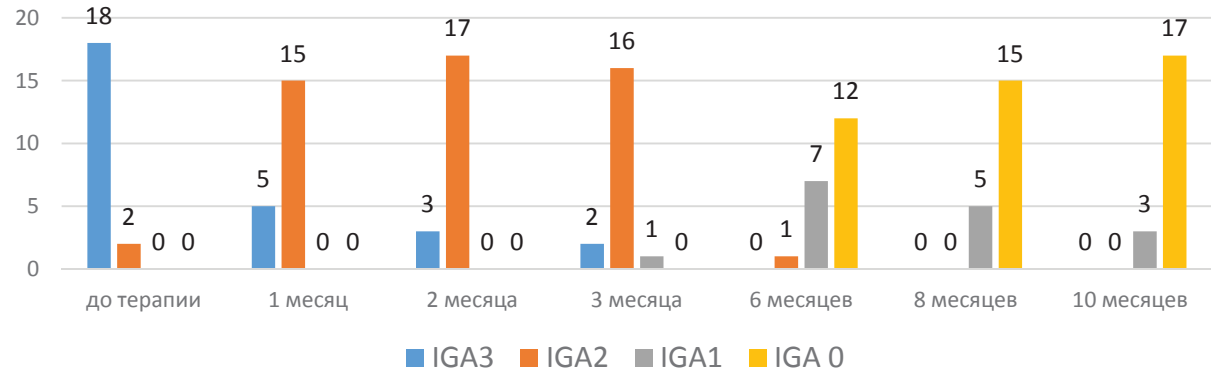


Figure 3. Details of clinical symptom changes (IGA) in Group 3 patients against the background of Verocutan® administration.

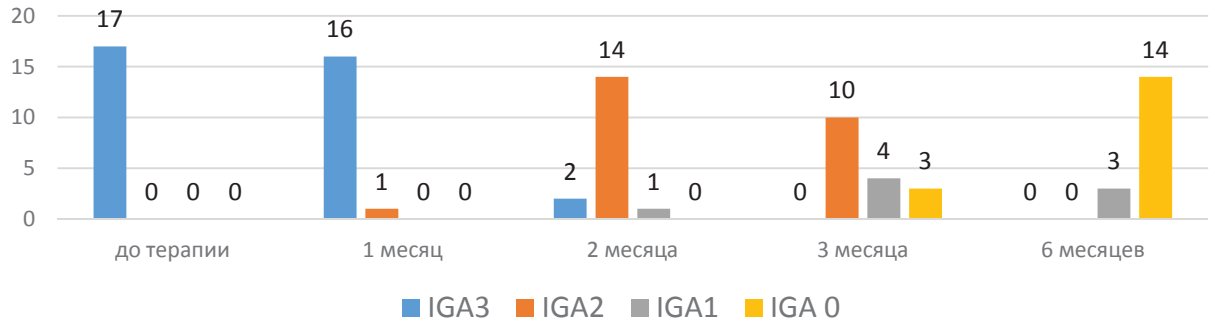


Figure 4. Details of clinical symptom changes (IGA) in Group 4 patients against the background of Verocutan® administration.

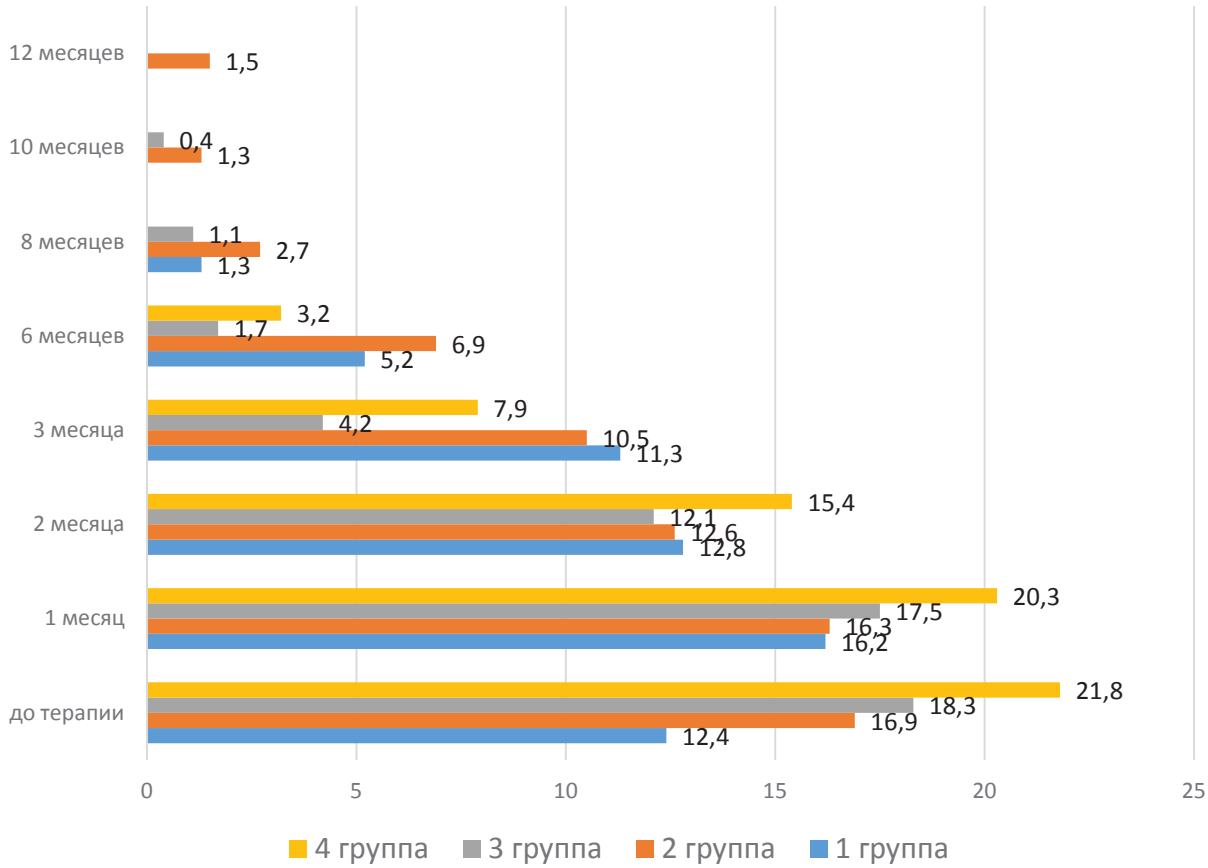


Figure 5. Details of DQoL index (point) changes in patients with acne against the background of Verocutan® administration.

Proportion of patients with achieved IGA 0 effect in Group 1 (n=21) in 6 months was 9.5%, in 8 months - 52.4%, in 10 months - 85.7%, and in 12 months - 90.5% (Figure 2). Thus, in patients with severe acne, "clear" skin (IGA 0) and "almost clear" skin (IGA 1) achievement was comparable with Group 1 patients, but developed later, which justifies the necessity of long-term cycles (>6 months) in this patient category.

Proportion of patients with achieved IGA 0 effect in Group 3 (n=20) in 6 months was 60.0%, in 8 months - 75.0%, in 10 months - 85.0% (Figure 3). Thus, in patients with moderately severe acne, "clear" skin (IGA 0) and "almost clear" skin (IGA 1) achievement was comparable with Group 1 patients.

Proportion of patients with achieved IGA 0 effect in Group 4 (n=17) in 6 months was 82.4% (Figure 4). Thus, in patients with excoriated acne, "clear" skin (IGA 0) and "almost clear" skin (IGA 1) achievement was comparable with Group 1 patients.

Changes of QoL index depended on the patient's age and disease severity (Figure 5). Before treatment, the most significant negative disease impact on quality of life was detected in the group of patients with excoriated acne (Group 4) - 21.8±1.3 points; in patients with moderately severe adult acne, parameters were worse (18.3±1.1) than in juvenile acne (12.4±2.3). According to changes of DQoL index in Group 1, deterioration was detected 1 month later - the index increased by 30.6%, which was likely related to overestimated effect expectancy or development of predictable side effects, although changes were positive in both groups. At the end of treatment cycle, the index decreased in Group 1 by 89.5%, in Group 2 – by 91.1%, in Group 3 – by 97.8%, in Group 4 – by 85.3% (Figure 5).

The main pathological event in acne is sebum hyperproduction. The study analyzed the evaluation of sebumetric values in patients depending on isotretinoin administration regimens (Table 2). Statistically significant changes in Groups 1, 3, 4 were obtained already after a single month of treatment ($p<0.05$). After 3 months of treatment, changes in all groups exceeded 50%, and the values were normal.

Skin moisture before treatment was decreased, mainly in patients with adult acne ($p<0.05$). After 1 month of treatment, despite regular use of specialized cosmetics, the parameter significantly decreased by 26.1-36.9% ($p<0.05$). Moisture recovery was detected from the 3rd month of treatment, and at end of treatment it was either normal or increased (Group 4) (Table 3).

During safety monitoring, which included blood biochemistry test (before treatment, 2 and 6 months after the onset of treatment), AST, ALT, alkaline phosphatase, triglyceride parameters tended to increase in 3-6 months in several (20.0%) Group 2 patients, but baseline values were exceeded by maximum 20%, which confirms dose-dependent direct correlation (in this group, patients were administered 0.8-1.0 mg/kg isotretinoin for 2-6 months, with subsequent dose decrease). These negative changes did not require drug discontinuation.

The following adverse events were detected during months 1-2: xerosis (45.8%), cheilitis (22.9%), mucosal dryness (13.3%), retinoid dermatitis (9.6%); they were infrequently observed due to low doses during the 1st month (Groups 1, 3, 4) and the use of specialized cosmetics, being predominantly registered in Group 2 patients (0.8-1.0 mg/kg dose).

Table 2

Changes of sebumetric parameters against the background of Verocutan® administration in various doses

Group/ age-specific normal values	Before treatment	1 month / changes	2 month / changes	3 month / changes	End of treatment (6-12 months) / changes
Group 1/49.6±5.7	89.6±10.2*	70.3±5.1**/21.5%	61.3±8.2**/31.6%	41.5±10.7**/53.7%	40.6±6.3**/54.7%
Group 2/49.6±5.7	92.3±7.8*	85.5±8.2/7.4%	70.3±5.4**/23.8%	40.8±11.4**/55.8%	41.8±5.7**/54.7%
Group 3/38.4±6.9	78.4±10.7*	55.2±11.6**/29.2%	40.1±8.2**/48.6%	32.4±5.9**/58.5%	30.6±2.4**/60.8%
Group 4/38.4±6.9	80.6±9.5*	65.6±8.7**/17.9%	42.4±5.8**/46.9%	33.6±5.1**/58.3%	31.3±4.9**/61.2%

Note: * compared with normal values, $p<0.05$ ** compared with values before treatment, $p<0.05$.

Table 3

Changes of corneometric parameters against the background of Verocutan® administration in various doses

Group/ age-specific normal values	Before treatment	1 month / changes	2 month / changes	3 month / changes	End of treatment (6-12 months) / changes
Group 1/ 66.7±8.9	65.1±2.3	41.0±2.6**/ -36.9%	40.3±2.5**/ - 38.1%	57.8±3.6**/ -11.2%	64.1±3.7/ -
Group 2/ 66.7±8.9	60.2±1.7	44.5±2.9**/ -26.1%	43.3±2.9**/ -28.1%	51.0±2.6**/ -15.3%	56.3±3.8/ -6.6%
Group 3/ 57.6±3.4	50.5±2.1*	31.4 ±2.5**/ -37.8%	29.5±2.3**/ -41.6%	33.7±2.5**/ -33.3%	51.7±4.1/ -
Group 4/ 57.6±3.4	49.4±2.1*	33.6±2.4**/ -31.9%	29.7±3.1**/ -39.9%	41.4±5.8/ -15.5%	54.4±3.5/ +9.2

Note: * compared with normal values, $p<0.05$ ** compared with values before treatment, $p<0.05$.

Conclusions

1. Isotretinoin (Verocutan®) administered in various doses decreases sebum production (according to sebumetric data) on average by 50% in 3 months. Low isotretinoin doses (0.2-0.3 mg/kg) during the first month in patients with moderately severe acne and during the whole therapy cycle in patients with excoriated acne, as well as the use of specialized cosmetics allow to decrease the frequency and severity of predictable side effects (xerosis, cheilitis, retinoid dermatitis).

2. 0.5 mg/kg Verocutan® is recommended for administration in moderately severe juvenile and adult acne, with treatment duration of 8-10 months (during the first month, isotretinoin 20 mg may be administered to decrease the severity of predictable side effects).

3. 0.8-1.0 mg/kg Verocutan® is recommended for administration in severe acne; if persistent clinical effect (IGA 1) is achieved during one month, isotretinoin dose can be decreased by 10 mg (in daily equivalent) every 2-3 months. Recommended treatment duration is 12 months.

4. Low-dose regimen is recommended for patients with excoriated acne (0.2-0.3 mg/kg during the whole treatment cycle of 6 months).

5. Verocutan® in patients with moderate-to-severe acne is well tolerated and can be considered safe. Skin and mucosal adverse events are quite frequent, but transient (their severity significantly decreases when using low doses (0.2-0.3 mg/kg) during the 1st month of treatment in patients with moderately severe acne); they can be well-controlled with topical moisturizers and do not require drug discontinuation.

Reference

1. Gollnick H. Acne and related disorders. In: Elzouki AY, Harfi HA, Nazer H, Oh W, Stapleton FB, Whitley RJ., editors. Textbook of Clinical Pediatrics. Berlin: Springer; 2012. p. 1447-1466.

2. Zouboulis CC, Baron JM, Böhm M, Kippenberger S, Kurzen H, Reichrath J et al. Frontiers in sebaceous gland biology and pathology. Exp Dermatol. 2008; 17 (6):542–551. doi: 10.1111/j.1600-0625.2008.00725.x.

3. Svirshchevskaya E.V., Matushevskaya E.V. Combined topical retinoids in acne therapy. Cons. Medicum. 2011; 3: 3–8 [in Russian].

4. Thiboutot DM, Knaggs H, Gilliland KL, Hagari S. Activity of type 1 5 alpha-reductase is greater in the follicular infra infundibulum compared with the epidermis. Br. J. Dermatol. 1997; 136 (2): 166–171.

5. Zouboulis CC, Katsambas A, Kligman AM. Pathogenesis and Treatment of Acne and Rosacea. Berlin, Heidelberg: Springer; 2014. p. 768.

6. Webster GF, Rawlings AV. Acne and its Therapy. 2007; 1: 336.

7. Picardo M, Picardo M, Ottaviani M, Camera E, Mastrofrancesco A. Sebaceous gland lipids. Dermatoendocrinol. 2009; 1(2): 68–71.

8. Harder J, Meyer-Hoffert U, Wehkamp K, Schwichtenberg L, Schröder JM.. Differential gene induction of human beta-defensins (hBD-1, -2, -3, and -4) in keratinocytes is inhibited by retinoic acid. J. Invest. Dermatol. 2004;123 (3): 522–529.

9. Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ et al. Inflammatory events are involved in acne lesion initiation. J Invest Dermatol. 2003; 121 (1): 20–27.

10. Zhang L, Li WH, Anthonavage M, Pappas A, Rossetti D, Cavender D et al. Melanocortin-5receptor and sebogenesis. Eur J Pharmacol. 2011; 660 (1): 202–206. doi: 10.1016/j.ejphar.2010.10.100.

11. Piérard-Franchimont C, Piérard GE, Saint-Léger D, Lévêque JL, Kligman AM. Comparison of the kinetics of sebum secretion in young women with and without acne. Dermatologica. 1991; 183 (2): 120–122.

12. Yamamoto A, Takenouchi K, Ito M. Impaired water barrier function in acne vulgaris. Arch Dermatol Res. 1995; 287 (2): 214–218.

13. Thiboutot DM, Dréno B, Abanmi A, Alexis AF, Araviiskaia E, Barona Cabal MI et al. Practical management of acne for clinicians: an international consensus from Global Alliance to improve outcomes in acne. J Am Acad Dermatol. 2018; 78: 1-23. doi: 10.1016/j.jaad.2017.09.078.

14. Gollnick HP, Buer J, Beissert S, Sunderkatter C. VerantwortlicherUmgang mit Antibiotika: Notwendigkeit der Antibiotikareduktionin der Aknetherapie. J. Dtsch. Dermatol. Ges. 2016; 14:1319-1327.

15. Tan J, Knezevic S, Boyal S, Waterman B, Janik T. Evaluation of evidence for acne remission with oral isotretinoin cumulative dosing of 120-150 mg/kg. J Cutan Med Surg. 2016; 20: 13-20.

16. Dréno B, Bettoli V, Ochsendorf F, Perez-Lopez M, Mobacken H, Degreef H et al. An expert view on the treatment of acne with systemic antibiotics and/or oral isotretinoin in the light of the new European recommendations. Eur J Dermatol. 2006;16: 565-571.

17. Rademaker M. Making sense of the effects of the cumulative dose of isotretinoin in acne vulgaris. Int J Dermatol. 2016; 55: 518-523. doi: 10.1111/ijd.12942.

18. Otchet «Otkrytoyerandomizirovannoye, perekrestnoye issledovaniye sravnitel'noyfarmakokinetiki i bioekvivalentnosti preparatov Vero-izotretinoin,kapsuly, 20 mg (OAO «Verofarm», Rossiya) i Roakkutan, kapsuly 20mg («R.P.Sherer», Germaniya) (An open, randomized, cross-sectional study of the comparative pharmacokinetics and bioequivalence of Veroisotretinoin preparations, capsules, 20 mg (OJSC «Veropharm», Russia) and Roaccutane, capsules 20 mg (R. P. Scherer, Germany))». SPb; 2012. p. 29 [in Russian].

Corresponding author
Kruglova Larisa
cgma-derma@yandex.ru