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Rare cases of Peutz–Jeghers syndrome in children

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Peutz–Jeghers syndrome is a genetic disease in which hamartomatous polyps of the gastrointestinal tract are detected, which leads to an elevated risk of developing colon cancer and other organs.

Aim: to determine the possibility of early diagnosis of Peutz–Jeghers syndrome in children.

The authors of the article present their **clinical observations** of patients with Peutz–Jeghers syndrome who were treated at Odesa Regional Children's Clinical Hospital. Retrospectively, over the past 20 years, according to the data of the Odesa Regional Children's Clinical Hospital, 2 patients with Peutz–Jeghers syndrome who were admitted to the hospital with acute abdominal syndrome were observed. The first case was a 5-year-old boy, who operated for the first time on ileoileal intussusception, resection of the small intestine with an end–to–end anastomosis. The second case was a 15-year-old girl, who operated on ileoileal intussusception, intestinal necrosis, peritonitis, and omentitis. Peitz–Jeghers syndrome was diagnosed after the first interventions.

Conclusions. Multiple polyps of the digestive tract are one of the causes of iron-deficiency anemia resistant to treatment with iron preparations, which requires the exclusion of Peutz–Jeghers syndrome. Abdominal pain syndrome in children requires a thorough family history, determination of phenotypic signs, and the appointment of a full clinical and instrumental examination. The suspicion of primary care physicians to the detection of phenotypic visual sign is a way to early diagnosis of possible Peutz–Jeghers syndrome; when detecting polyps of the digestive tract in a child during an endoscopic examination with histological examination of the removed polyp and the presence of phenotypic extraintestinal signs of Peutz–Jeghers syndrome.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the author.

Keywords: cases, Peutz–Jeghers syndrome, children.

Рідкісні випадки синдрому Пейтца–Єгерса в дітей

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Синдром Пейтца–Єгерса – це генетичне захворювання, за якого виявляються гамартомні поліпи шлунково-кишкового тракту, що призводить до підвищеного ризику розвитку раку кишечника та інших органів.

Мета: проаналізувати можливості ранньої діагностики синдрому Пейтца–Єгерса в дітей.

Наведено власні **клінічні спостереження** хворих із синдромом Пейтца–Єгерса, які перебували в Одеській обласній дитячій клінічній лікарні. Згідно з даними обласної дитячої клінічної лікарні м. Одеса, за останні 20 років ретроспективно під спостереженням було 2 хворих з синдромом Пейтца–Єгерса, які надійшли в лікарню з гострим абдомінальним синдромом. Перший випадок – хлопчик 5 років, оперований вперше з приводу тонко-тонкокишкової інвагінації, резекції тонкої кишки з анастомозом «кінець–в–кінець». Другий випадок – дівчина 15 років, оперована з приводу тонко-тонкокишкової інвагінації, некрозу кишки, перитоніту, оментиту. Синдром Пейтца–Єгерса встановлено після перших втручань.

Висновки. Однією з причин розвитку залізодефіцитної анемії, резистентної до лікування препаратами заліза є множинні поліпи травного тракту, що потребує виключення синдрому Пейтца–Єгерса. Больовий абдомінальний синдром у дітей потребує ретельного збору сімейного анамнезу, визначення фенотипових ознак та призначення повного клініко-інструментального обстеження. Настороженість лікарів першої ланки до виявлення фенотипової візуальної ознаки – шлях до ранньої діагностики можливого синдрому Пейтца–Єгерса; після виявлення в дитини поліпів травного тракту під час проведення ендоскопічного обстеження варто звернути увагу на результат гістологічного дослідження вилученого поліпу та наявність фенотипових позакишкових ознак синдрому Пейтца–Єгерса.

Дослідження виконано відповідно до принципів Гельсінської декларації. На проведення досліджень отримано інформовану згоду пацієнтів. Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: випадки, синдром Пейтца–Єгерса, діти.

Peutz–Jeghers syndrome (PJS) is a genetic disorder that causes hamartomatous polyps of the gastrointestinal tract, which leads to an elevated risk of developing colon cancer and other organs.

Peutz–Jeghers syndrome was first described in detail by a Dutch physician John Peutz in 1921, based on the observation of three family members with facial pigmentation combined with intestinal polyposis. It was he who suggested that the disease was hereditary. A quarter of a century later, in 1949, the American physician Harold Jeghers and co-authors described 10 cases of this disease and identified a specific triad: gastrointestinal polyposis, the hereditary nature of the disease, and pigmented spots on the skin and mucous membranes [1,6,11].

PJS-type hamartomatous polyps are most commonly found in the small bowel (in order of preva-

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lence: jejunum, ileum, and duodenum), but can also occur in the stomach, colon, and extraintestinal areas, including the renal pelvis, bronchi, gallbladder, bladder and ureters. Gastrointestinal polyps can lead to chronic bleeding, anemia, recurrent obstruction, and intestinal invasion, requiring repeated laparotomy and bowel resection [1,2].

The disease is caused by an inherited mutation in the *STK11* gene, also known as the *LKB1* gene. The *STK11* gene encodes serine/threonine kinase 11, which is involved in the regulation of cell division and apoptosis. Mutations of the *STK11* gene result in a complete cessation or dysfunction of protein production and uncontrolled cell growth, which, as a result, causes the development of hamartomatous polyps and cancer [3,4,7].

However, about 50% of patients have no family history – in these cases, a *de novo* mutation of the *STK11* gene is assumed to have arisen in the germ cells. The defective allele is transmitted to half of the patient's descendants regardless of gender. Nevertheless, people with this diagnosis are seriously ill, as they have a significantly elevated risk of stomach, pancreatic, colon, small bowel, and bladder cancer [1,3,7].

Macroscopic visualization of polyps is performed endoscopically or intraoperatively. They can be flat or tall, of different sizes (from a few millimeters to 5 centimeters or more), with a smooth or lobulated surface, with a wide base and a pedicle. Hamartomas are located singly or in clusters, sometimes lining the entire surface of the mucous membrane, resembling a carpet [4,7].

Microscopic examination of hamartomas reveals excessive stromal development, disturbance of the ratio of tissue elements in the absence of activation of proliferative processes, and cellular atypia on the part of the epithelial layer. The basis of these changes is the prolapse of the muscular layer of the mucosa's lamina propria into the polyp stroma with tree-like branching of smooth muscle fibres, which, when examined morphologically, creates a false impression of epithelial invasion into the intestinal wall [2,3].

Peutz-Jeghers syndrome is also called polyp and spot syndrome. A specific extraintestinal symptom of PJS is pigmentation of the skin and mucous membranes. Dark brown or black spots up to 2–5 mm round or oval in shape are found on the face, mouth, palms, feet, forearms, and nails. Groups of rashes can be located in separate clusters. Localization of lentigo in the oral cavity is a hallmark of PJS. They are unevenly distributed over the gums, cheek mucosa, and hard palate [1,2].

The most common complaint in these patients is signs of acute abdominal syndrome. The reason for hospitalization of a child is recurrent colic and abdominal pain, signs of gastrointestinal bleeding (melena, bloody vomiting), intestinal intussusception with intestinal obstruction, and chronic anemia [9,13].

The diagnosis of the syndrome is based on the clinical features of the disease and, if necessary, is confirmed by molecular genetic testing to detect a mutation in the *STK11* gene. A full blood cell count, fecal examination, fecal occult blood test, and carcinoembryonic antigen test are performed.

Imaging of tumours includes capsule endoscopy, magnetic resonance imaging, virtual computed tomography, and endoscopic examination methods. The diagnosis is considered reliable if at least one of the following signs is present [10]:

— two or more histologically confirmed hamartomatous polyps;

— hereditary history of polyps;

— definitive pigmentation of the skin and mucous membranes combined with a burdened hereditary history of PJS.

Since pigmentic spots are benign lesions, they do not require treatment. The cosmetic defect can be hidden by cosmetic means.

The main method of treating polyposis is surgery. The treatment is based on preventive polypectomy of polyps larger than one centimeter using endoscopy and imaging techniques to avoid symptoms associated with their growth. Surgical resection is necessary when polyps cannot be removed endoscopically. Surgery is the most common treatment for intestinal intussusception caused by enlarged polyps, but in some cases, endoscopic resection is possible after removing intussusception with balloon endoscopy [8,14,15].

This strategy has two objectives:

— to reduce complications of large polyps, such as bleeding, anemia, obstruction, and intestinal obstruction;

— to reduce the risk of cancer development due to malignant transformation of PJS-type polyps.

The aim of the study**:** to investigate the possibility of early diagnosis of Peutz-Jeghers syndrome in children.

Retrospectively, over the past 20 years, according to the data of the Odesa Regional Children's Clinical Hospital, 2 patients with PJS who were admitted to the hospital with acute abdominal syndrome were observed. The examination results revealed PJS. All

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children underwent a full general clinical and instrumental examination (ultrasound, abdominal X-ray).

We present our clinical observations of patients with PJS who were treated at Odesa Regional Children's Clinical Hospital.

The examinations were performed in accordance with the principles of the Declaration of Helsinki. The investigation protocol was approved by the Local Ethical Committee of all involved institutions. The informed consent of the children's parents was obtained for conducting the study.

Clinical case 1

A 5-year-old boy was admitted to the surgical inpatient department with symptoms of invagination (colicky abdominal pains for several days, vomiting). Objectively, the child is in a severe condition, the skin is pale, and there are multiple small dark pigment spots on the oral mucosa and lips. The abdomen was bloated, painful to palpation, symptoms of peritoneal irritation and muscle defence were doubtful, and peristalsis was not heard. A survey radiograph of the abdominal cavity revealed single hydroaerial levels of different diameters in the mesogastrium. Preliminary diagnosis: acquired acute intestinal obstruction, peritonitis.

The child was operated on after preparation, and intraoperatively, an oncoming ileoileal intussusception was detected. An attempt to remove the intussusceptum is impossible due to changes in the intestinal wall. The intussusceptum was resected. During the revision of the intestine, multiple polyps of different sizes were detected, a part of the small bowel with a completely polyp-altered wall was removed (Fig. 1).

End-to-end intestinal anastomosis. The abdominal cavity was irrigated. The postoperative period was good, without complications. The histological examination confirmed intestinal polyposis. The cause of intussusception was «kissing» polyps.

In the postoperative period, a complete endoscopic examination was performed, and small polyps were found in the stomach, colon, and bladder. In addition, the boy had a typical phenotype – hyperpigmentation of the lips (Fig. 2). The family history revealed that the closest relatives in the family had colon cancer, breast cancer, and bladder cancer.

The diagnosis was made PJS, ileoileal intussusception, resection of the small bowel with an end–to–end anastomosis; and intestinal absorption disorder.

After that, the child was admitted to a surgical hospital and operated for an acute abdomen clinic

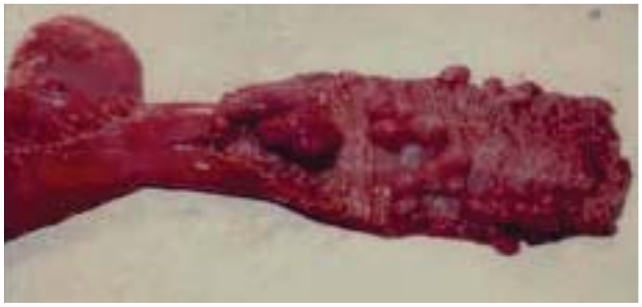

Fig. 1. Specimen of the resected small bowel with multiple polyps of different size

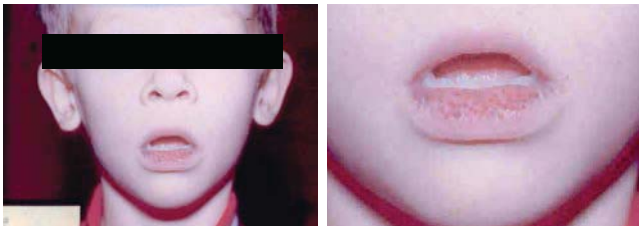

Fig. 2. Photo of the face of a boy with Peutz–Jeghers syndrome – hyperpigmentation of the red border of the lips (own observation)

Fig. 3. Photo of the face of the girl with Peutz–Jeghers syndrome (own observation)

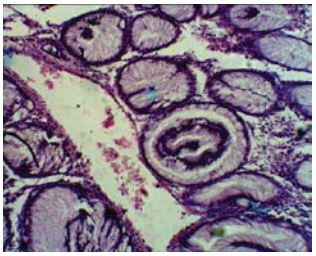

Fig. 4. Glandular polyp. Hematoxylin-eosin staining. ×100

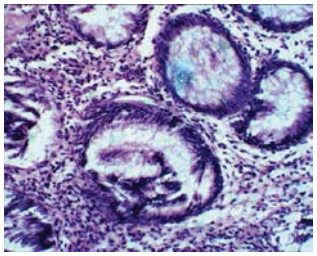

Fig. 5. Inflammatory infiltrate in the polyp tissue. Hematoxylin-eosin staining. ×200

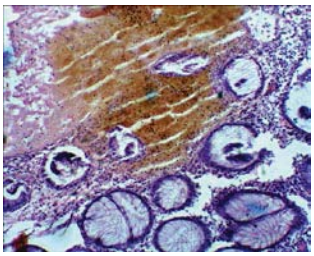

Fig. 6. Hemorrhage into the polyp tissue. Hematoxylin-eosin staining. ×100

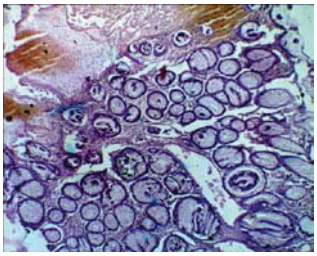

Fig. 7. Polyp of the small bowel. Hematoxylin-eosin staining. ×40

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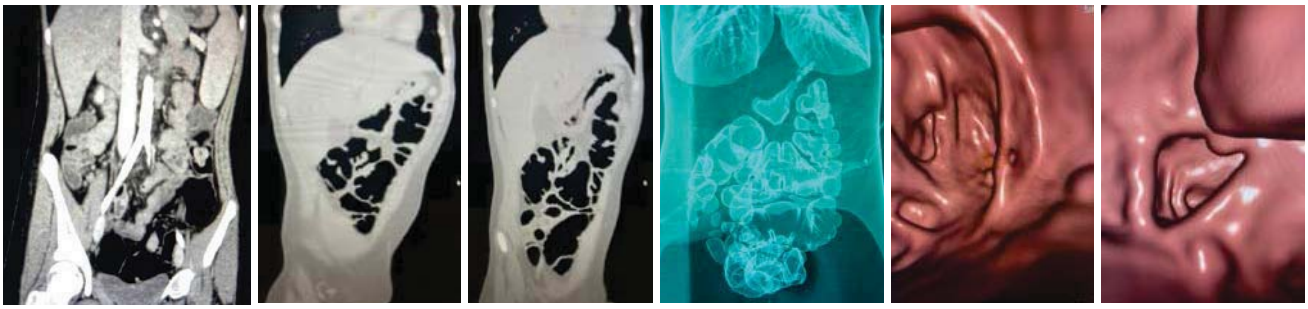

a) b) c d) e) f)

Fig. 8. Multispiral computed tomography: numerous polyps in the intestinal lumen. The colon walls are not thickened, but in all sections, there are polyps with a diameter of 3 to 9 mm, located on relatively wide legs, reliably no areas of violation of their integrity were detected: a – coronal slice of the arterial phase of the scan; b, c – use of multi-planar reconstruction and projection of the most intense signal to assess changes in the intestine; d – use of 3D reconstruction; e, f – examination of the intestine in the virtual colonoscopy mode

(acute obstruction) six times. Due to a significant reduction of the intestine, the absorption processes were impaired, and the boy lagged behind his peers in physical development.

We followed the boy until he was 18 years old. Then we lost contact with him.

Clinical case 2

A girl born in 2007 had complaints of recurrent abdominal pain, eating disorders, and sometimes vomiting for several years. Her mother repeatedly visited a pediatrician and a gastroenterologist with complaints of abdominal syndrome. The child underwent a limited examination (general tests, abdominal ultrasound), and was prescribed symptomatic therapy, which was ineffective. No attention was paid to the phenotypic features of the face. In November 2022, the girl was hospitalized with acute abdominal syndrome: colicky abdominal pains, repeated vomiting, and fever. The child's condition was severe, the skin and mucous membranes were pale, the tongue was coated, and skin turgor was reduced. The abdomen was tense, there were positive symptoms of peritoneal irritation and muscle defence throughout the abdomen. An X-ray revealed single hydroaerial levels in the meso- and hypogastrium. Abdominal ultrasound showed fluid and suspected intussusception. After preoperative preparation, the child was operated on. Intraoperatively, ileoileal intussusception, intestinal necrosis, peritonitis, and omentitis were detected. A resection of the small bowel due to necrosis, end-to-end anastomosis, resection of the large cecum; wedge resection of the small bowel with removal of the polyp; irrigation and drainage of the abdominal cavity were performed. Macroscopic examination revealed multiple polyps, some of them on the pedicle, ranging in size from 3 mm to 1.5 cm. The next day, lip pigmentation was noticed (Fig. 3). PJS was suspected.

Histological examination of the removed part of the intestine revealed the following: intestinal wall with unevenly developed vessels, and granulation tissue. Hemorrhages, small bowel with hyperplastic cystic glands, the presence of smooth muscle cell bundles in the stroma with small hemorrhages, and uneven lympholeukocytic infiltration (Fig. 4–7).

In the postoperative period, the girl underwent a full clinical examination to confirm the diagnosis, including a virtual computed tomography-colonoscopy, endoscopy of the upper digestive tract, and genetic karyotyping.

Virtual computed tomography-colonoscopy is a non-invasive method of examining the large bowel based on imaging using modern X-ray multislice tomography in 3D imaging mode. This study revealed numerous polyps with pedicles in the colon lumen without signs of erosion (Fig. 8). There were no signs of obstruction. An endoscopy of the stomach revealed scattered small foci of lymphofollicular hyperplasia. Along the large curvature, there were polyp-like whitish elastic formations on a wide base, up to 2.5–3.0 mm in diameter. There are two polyps 2.0–2.5 mm in diameter along the posterior wall and three more polyps on a wide base 3.5–4.0 mm in diameter below. The folds are moderately thickened, and tortuous.

Cytogenetic analysis of 20 metaphase plates revealed a normal female karyotype (Fig. 9). In our case, the girl belongs to the category of patients in whom PJS was diagnosed *de novo*.

Additionally, the girl's laboratory tests revealed iron-deficiency anemia (ferritin 6.6 ng/mg), vitamin D deficiency (17.8 ng/ml), and B_9 deficiency (3.4 ng/ml).

Postoperative diagnosis: intestinal polyposis (PJS); ileoileal intussusception, intestinal necrosis; omentitis; postoperative intestinal absorption disorder.

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But perhaps this operation could be avoided if a routine examination was carried out in time and specific phenotypic sign was taken into account.

Discussion

According to the World Health Organization criteria, if:

— cases of PJS have been identified in the family, any number of histologically verified polyps and pigmentation of the skin and mucous membranes will indicate the disease;

— the family history of PJE is absent, at least 3 histologically verified polyps or pigmented skin and mucous membranes specific for the disease should be detected [14,15].

Even if genetic tests are available to detect the *LBK1/STK11* gene, negative results do not exclude the diagnosis, as not all genetic mechanisms involved in this syndrome have been discovered [3,4,7].

Polyps grow in the first decade of life, and most patients develop symptoms between the age of 10 and 30 years old. In a number of cases, the most common gastrointestinal symptoms were: obstruction caused by intestinal intussusception or lumen occlusion by polyps (43%), abdominal pain (23%), acute or chronic rectal bleeding (14%), and polyp extrusion through the rectum (43%). In 69% of patients, intestinal intussusception occurs during their lifetime, and this problem is more common in the small bowel [1,2].

PJS is associated with an elevated risk of gastrointestinal and non-gastrointestinal malignancies. Meta-analysis showed a cumulative risk of 93% for all types of malignancies in the age group 15 to 64 years. Thus, a relative risk of developing neoplasia in a person with PJS in any region is up to 15 times higher than in the general population [5,10].

Such risks justify the search for polyps in the small and large bowel from childhood with polypectomy for polyps larger than 5 mm. The use of capsule endoscopy is considered a good method of searching in the small bowel, but a less sensitive option is computed tomography with per oral contrast. Double-balloon enteroscopy is an excellent option if associated with therapeutic treatment. However, this procedure is very invasive for monitoring or scanning procedures.

Colonoscopy, endoscopy, computer tomography (CT), magnetic resonance imaging (MRI) or ultrasound of the pancreas, chest X-ray, mammography and pelvic ultrasound in women, testicular examination in men, and levels of CA-19-9 and CA-125 are recommended.

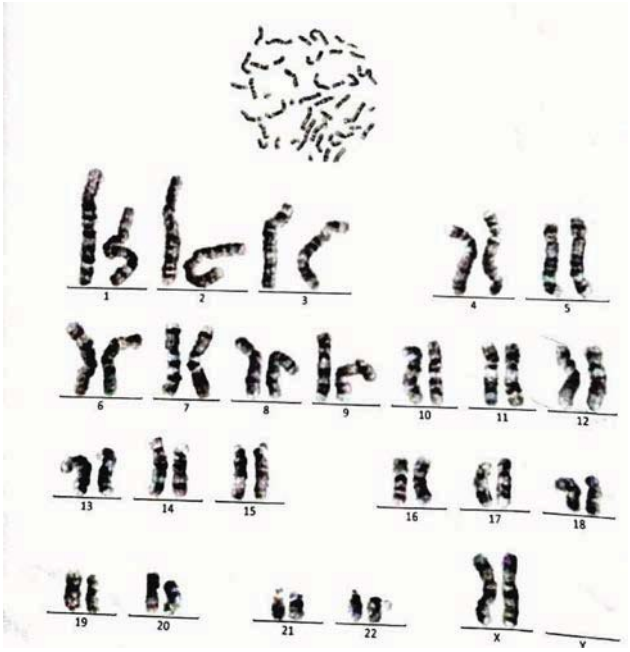

Fig. 9. Result of the child's cytogenetic analysis

In cases where the disease is complicated by intussusception, a partial bowel resection or enterotomy with polypectomy is required. There is evidence that polyp removal prevents emergency laparotomy and neoplasia progression and increases the time without surgery [9,13].

There is still no pharmacological treatment. Studies show the role of chemoprophylaxis with rapamycin or nonsteroidal anti-inflammatory drugs (due to the high activity of cyclooxygenase type 2 in polyps) [1,14].

PJS is associated with an elevated risk of cancer, mainly pancreatic and cervical cancer. This information is a useful source for improving current surveillance protocols [14,15].

Thus, the diagnostic key to PJS is a combination of phenotype and genotype with histological confirmation, namely the presence of distinctive pigmentation of the skin and mucous membranes, anamnestic heredity of the disease, and two or more histologically confirmed polyps of the digestive tract.

The phenotype is characterized by an early visual symptom, which makes it possible to recognize the syndrome by prescribing timely examination and treatment long before complications occur. The main management measures are dynamic monitoring and prevention of complications. The main

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treatment is surgical. The main diagnostic methods are endoscopic. The cause of iron-deficiency anemia resistant to treatment with iron supplements is multiple polyps.

Conclusions

Despite the rarity of the syndrome in children, but taking into account the malignancy of the disease, we consider it appropriate to draw the following conclusions:

1. The suspicion of primary care physicians to the detection of a phenotypic visual sign, namely pigmentation of the mucous membranes and lips, is the way to early diagnosis of possible PJS.

2. When detecting polyps of the digestive tract in a child during an endoscopic examination, attention should be paid to the results of histological examination of the removed polyp and the presence of phenotypic extraintestinal signs of PJS.

3. Hematologists should remember that one of the causes of iron-deficiency anemia resistant to iron supplementation is multiple polyps of the digestive tract, which also requires the exclusion of PJE.

4. Abdominal pain syndrome in children requires a thorough family history, determination of phenotypic features, and a full clinical and instrumental examination.

No conflict of interests was declared by the authors.

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