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AICARDI–GUTIER SYNDROME IN A PATIENT WITH CEREBRAL PALSY

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Abstract. Rare genetic diseases and their symptoms are unusual for doctors, especially if the disease is heterogeneous, and this poses a serious medical problem. There are about 7000 different rare diseases in the world, 80% of them are genetically determined, and more and more newly discovered ones are appearing. Approximately 50% of patients suffering from rare diseases are children, which determines the importance of studying these diseases in pediatric science. On the example of a clinical case, the manifestations of the Aicardi–Goutieres syndrome in a 17-year-old child admitted to the St. Petersburg State Pediatric Medical University clinic with the main diagnosis: nephrotic syndrome with diffuse membranous glomerulonephritis are considered. The main data of history and clinical and laboratory examination are reflected. The description of mutations leading to the emergence of Aicardi–Goutieres syndrome, as well as the forms of this disease, is presented. Special attention is paid to the differential diagnosis of Aicardi–Goutieres syndrome with other clinically similar nosological forms.

Key words: *rare (orphan) diseases; Aicardi–Goutieres syndrome; AGS; children.*

СИНДРОМ АЙКАРДИ–ГУТЬЕРА У ПАЦИЕНТА С ДЕТСКИМ ЦЕРЕБРАЛЬНЫМ ПАРАЛИЧОМ

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Резюме. Редкие наследственные заболевания и их симптоматика являются необычными для врачей, особенно если заболевание гетерогенно, и это представляет серьезную медицинскую проблему. В мире существует около 7000 различных редких заболеваний, из них 80% — генетически детерминированы. Появляется все больше вновь обнаруженных орфанных болезней. Приблизительно 50% пациентов, страдающих редкими заболеваниями, — это дети, что обусловливает важность изучения данных болезней в педиатрической науке. На примере клинического случая рассмотрены проявления синдрома Айкарди–Гутьера у ребенка 17 лет, госпитализированного в клинику СПбГПМУ с основным диагнозом: нефротический синдром при диффузном мембранозном гломерулонефрите. Отражены основные данные анамнеза и клинико-лабораторного обследования. Представлено описание мутаций, приводящих к возникновению синдрома Айкарди–Гутьера, а также формы данного заболевания. Особое внимание отведено дифференциальной диагностике синдрома Айкарди–Гутьера с другими клинически схожими нозологическими формами.

Ключевые слова: *редкие (орфанные) заболевания; синдром Айкарди–Гутьера; AGS; дети.*

INTRODUCTION

Rare diseases have recently begun to attract the attention of doctors. Of the 7000 nosological forms, 80% of rare diseases are genetically determined, and 50% of those suffering from these diseases are pediatric patients [1]. About 30% of children with rare diseases do not survive beyond 5 years of age [10].

If a disease has a prevalence of 10 cases per 100 thousand population, it is classified as an orphan disease. All orphan diseases have a chronic lifelong course and often progressive nature [6]. For 2018–2020 there was an increase in the total number of patients due to almost all nosological forms of orphan diseases [13, 14]. Compared to 2019, in 2021 the budget for orphan diseases in Saint Petersburg has increased. The number of patients with a separate nosological form, idiopathic thrombocytopenic purpura, is 2 times higher than the average [13]. Due to the steady increase in rare congenital pathologies, it is necessary to ensure that children are protected from the severe consequences of such diseases.

In the Russian Federation, regulations have been developed governing the provision of assistance to patients suffering from rare diseases [9]. In particular, Decree of the President of the Russian Federation dated June 1, 2012 № 761 "On the national strategy of action in the interests of children for 2012–2017" emphasizes the importance of establishing a federal register of children with rare diseases and organizing targeted funding for such children at the expense of budgetary allocations of the federal budget according to this register [8]. There is also a departmental program "Improving the system of organizing medical care and drug provision for citizens suffering from diseases included in the list of life-threatening and chronic diseases", the indicators of which in the "pediatrics" section are: reduction in mortality and disability of children under 18 years of age suffering from these diseases, increase their life expectancy and improvement of their quality of life. An important document is the Order of the President of the Russian Federation V.V. Putin dated January 16th, 2014 № Pr-78 "On the concept of providing early assistance to children with genetic disorders" [12].

Rare diseases are characterized by non-specific symptoms, manifestation of signs at different age periods, progressive nature, and also require careful differential diagnosis with clinically similar pathologies. These factors make diagnosis difficult and can lead to delays in providing medical care. Issues of drug provision for patients suffering from orphan diseases are very complex due to the high cost of necessary therapy and limited budgetary funds. The lack of necessary therapy leads to a reduction in the life expectancy of patients, and in some cases, to death [11]. Complex diagnostics, absence of a unified comprehensive strategy for providing medical assistance to patients with orphan diseases, and the severe consequences of diseases without timely treatment determine the relevance of studying rare diseases at the present time. A solution to this problem can be neonatal screening for orphan diseases.

We present a case of Aicardi–Goutières syndrome (ICD-10 code G31.8), which is classified as an orphan disease based on the List of Orphan Diseases of the Russian Ministry of Health [7] in a 17-year-old child to illustrate the importance of studying rare diseases.

CLINICAL CASE

For examination and determination of tactics for further management, a young man with periodic proteinuria for 10 years (since 2013) was hospitalized in the department of the Saint Petersburg State Pediatric Medical University clinic in a planned manner. Upon admission, a preliminary diagnosis was made: nephrotic syndrome with diffuse membranous glomerulonephritis.

A disabled child (cerebral palsy, spastic diplegia, flexion contractures in the knee joints) is on the dispensary of a neurologist due to Aicardi-Goutières syndrome, which is inherited in an autosomal dominant mode. The child has spastic tetraparesis with predominantly damage to the lower extremities, hyperkinetic syndrome, cognitive disorders, psychovegetative syndrome with cerebrovascular disorders, migraine-like headaches. As a treatment for hyperkinetic syndrome, he receives a centrally acting muscle relaxant (tizanidine or sirdalud). The orthopedist diagnosed kyphoscoliosis, lower extremity joint contractures, valgus deformity of the left foot, cavovalgus deformity of the right foot, deformity of the first fingers and toes, rotational displacement of C_1. Due to subclinical hypothyroidism diagnosed by an endocrinologist, he receives L-thyroxine. Suffers from myopia, astigmatism, nosebleeds. The patient has stage 2 secondary arterial hypertension; during dynamic observation, episodes of increased pressure up to 170/90 mmHg are noted. Chronic tonsillitis. Childhood infections denied, negative tuberculosis anamnesis, injuries denied.

From the anamnesis collected from the words of the grandmother and from the presented medical documentation, it is known: the mother of the child has spastic paraparesis since the age of 4, is

intellectually intact, the father has cerebral palsy. A child from the first pregnancy, the first emergency delivery by cesarean section, birth weight 2450 g, height 47 cm, discharged from the maternity hospital on the 7th day, artificial feeding. In the first days of life hyperkinesis the lower extremities was noted; he crawled from 8 months, sat from 8–9 months, and began to walk from 1 year 2 months. At the age of 1 year 4 months, febrile tonic-clonic seizures appeared and were reduced independently. From this moment on, a rapid progression of the lower extremity spasticity, the formation of paraparesis, and regression of neurological skills were noted. Febrile seizures repeated twice, after which the acquired skills were lost. Further rate of development: rolls over from 2.5 years old, crawls from 3 years old, sits from 4 years old, walks with support from 4 years old. Since 2010, blood tests have consistently shown high ESR levels. In 2013, proteinuria was detected for the first time. In 2014, he underwent surgical treatment at H.Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery — adductor tenotomy tenomyotomy with cutting of the tendinous portion of the *m. iliopsoas*, lengthening of the tibia flexors on both sides. Arthrodesis of the talonavicular joint on the right. Due to the appearance of fever, proteinuria, and elevated ESR, he was transferred to the specialized department of the Saint Petersburg State Pediatric Medical University clinic. Ultrasound revealed renal pelvis dilatation on the left, without signs of vesicoureteral reflux. Subsequently, the elevation of ESR remained, proteinuria constantly observed in urine tests up to a maximum of 5 g/day. Proteinuria without impairment of renal function was detected. Subsequently, the increase in ESR and proteinuria in urine tests remained constant, up to a maximum of 5 g/day. In 2017, an MRI of the brain was performed – low lying cerebellar tonsillar position. An MRI of the brain in 2021 revealed basal ganglia calcifications up to 5 mm in size in the substance of both frontal lobes. Enlarged perivascular spaces are identified in the basal ganglia. According to the results of a genetic research for the "neurodegenerative diseases" block, a variant with an unknown clinical significance c.2636A>G of the IFIH1 gene in a heterozygous state was identified. The child's mother was detected the same genetic variant in a heterozygous state. The child was consulted by a geneticist: Strumpell's disease was excluded, as well as Singleton–Merten syndrome 1, associated with mutations in this gene, but the clinical picture was not consistent with this disease. Taking into account the genetic variant, clinical picture data, and MRI of the brain, this case may correspond to the diagnosis of Aicardi–Goutières syndrome 7; no increased level of interferon-α was detected.

Objective status. The condition is of moderate severity due to the neurological manifestations of cerebral palsy. Contactable, answers questions. Well-being is satisfactory. Forced position in bed, sits up independently, turns himself in bed with support on his hands. There are no complaints at the time of examination. The skin is clean, regular coloring, and there is no infectious rash. Peripheral edema is absent. Visible mucous membranes are clean. Peripheral lymph nodes are not enlarged. The pharynx is not hyperemic. Nasal breathing is free. Respiration is vesicular, carried out in all lung fields; there are no abnormal respiratory sounds or wheezing. The peripheral pulse in the peripheral arteries is satisfactory in all respects. Heart sounds are clear, rhythmic, sonorous, they are heard over the entire surface of the heart, the ratio of sounds is correct, there are no additional muscle sounds, there is no splitting or bifurcation of tones at the 2nd and 3rd points of auscultation, extracardiac murmurs are not heard. Temperature — 36.6 °C. Heart rate — 80 beats/min. Blood pressure — 130/90 mm Hg. On palpation, the abdomen participates evenly in the act of breathing, soft, painless in all areas. The liver borders are normal. The spleen is not palpable.

Tapping in the lumbar regions is negative on both sides. Urination is free, painless, there is no dysuria. Diuresis is sufficient. The stool is regular and formed. Joint status: all joints are not warm, soft nodules are palpable above the joints of the first fingers and metacarpophalangeal joints of the second fingers of both hands, the range of motion in the joints is not limited. The lower limbs are in a forced position, the knee joints are straightened, the ankle joints are in plantar flexion.

The physical development of the patient was assessed, taking into account motor activity and diagnosed cerebral palsy GMFCS III, as well as the component composition of the body using bioimpedance analysis (Fig. 1).

In consideration of the family anamnesis, clinical picture, MRI and genetic research data, the patient was prescribed a coagulogram with a lupus anticoagulant test in order to exclude monogenic variants of systemic lupus erythematosus.

Based on the results of an examination of the patient by a nutritionist, mild protein-energy malnutrition was detected, corrected using a formula (+500 kcal). For 6 years, the child received subsidies with Modulen IBD formula in a volume of 500 ml in fractional per day. Body weight 39.4 kg, height 155 cm (calculated using the leg method), BMI = 16.40, which is below normal.

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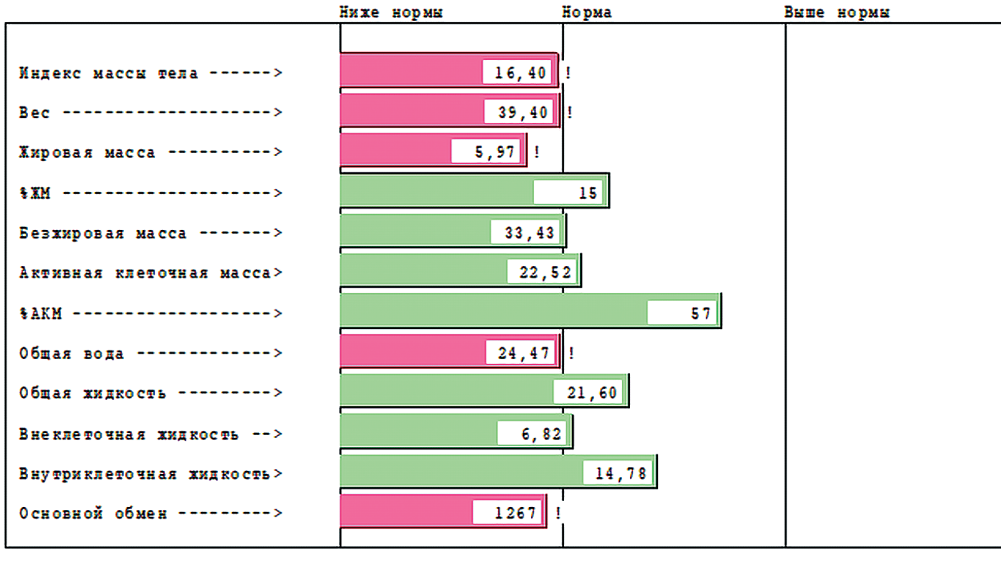

ПОКАЗАТЕЛЬ		Должные	% долж.	Измерен.	% измер.	Отклон.	%от долж
ИМТ	(кг/м2.)	18,53		16,40			
Вес	(кг)	44,51	100,00	39,40	100,00	-5,11	-11,48
ЖМ	(кг)	7,50		5,97		-1,53	-20,43
%ЖМ	(%)	17		15			
БЖМ	(кг)	37,01	83,15	33,43	84,85	-3,58	-9,67
АКМ	(кг)	24,55		22,52		-2,03	-8,29
%АКМ	(%)	55		57			
ОВ	(л)	27,39	61,53	24,47	62,11	-2,91	-10,64
ООЖ	(л)	22,51		21,60		-0,90	-4,02
ОВнек.Ж.	(л)	7,50		6,82		-0,68	-9,09
ОВнук.Ж.	(л)	15,00		14,78		-0,22	-1,49
ОО	(ккал)	1481		1267		-215	-14,50

Fig. 1. Body Composition Data

Рис. 1. Данные компонентного состава тела

Antibodies to the herpes simplex virus, cytomegalovirus, and Epstein–Barr virus were not found. Total IgE levels are elevated. Antiphospholipid antibodies were not detected. No increase in the level of interferon-α was identified. The dynamics of the patient's laboratory examination parameters are presented in Table 1.

DISCUSSION

Aicardi–Goutières syndrome is a rare genetic disease. About 400 cases of the syndrome have been described in the world. Various names for the disease are mentioned in the literature: Aicardi–Goutier(es) syndrome, Aicardi–Gutier(es), Ekardi-Goutie(es). The article gives the name Aicardi–Goutières. Aicardi–Gouthières syndrome (AGS) is a genetically determined interferonopathy, a monogenic inflammatory encephalopathy caused by mutations in any of nine genes (*TREX1, RNASEH2A/B/C, SAMHD1, ADAR1, IFIH1, LSM11* and *RNU7–1*) encoding the proteins involved in nucleic acid metabolism and detection [15]. The disease is characterized by non-specific clinical manifestations. Most patients suffering from Aicardi–Goutières syndrome have neurological disorders of varying degrees: from spastic paraparesis with relatively preserved cognitive functions to tetraparesis and severe mental retardation [2]. 75% of patients develop epilepsy, which in half of the cases is resistant to therapy with a predominance of tonic-clonic seizures [4]. Interferonopathy is associated with early onset neurological disability and systemic inflammation. Taking into account that each AGS subtype has common characteristics, cases of varying severity of course and subsequent complications occur. However, regardless of the specific variant, all forms of the syndrome lead to increase in the level of interferon-α [16]. Because of this heterogeneity, it is important to fully characterize the trajectory of the syndrome [3]. Forms with the onset of the disease in the neonatal period are clinically more severe than forms with onset after the first months of a child's life, and are associated with high mortality (up to 34% in the first year of life). If the onset of the disease occurred after the first months of the child's life, such patients have a longer life expectancy and

Table 1. Indicators of laboratory observation of the patient

Таблица 1. Динамика показателей лабораторного обследования пациента

Параметр / Parameter	Референтный интервал / Referential interva	Даты проведения исследования / Dates of the study		
		30.08.2022	05.09.2022	09.09.2022
Лабораторные показатели крови / Laboratory blood parameters				
Лейкоциты, $\times10^9$/л / Leukocytes, $\times10^9$/L	4–9	6.40		11.90
Эритроциты, $\times10^{12}$/л / Red blood cells, $\times10^{12}$/L	4,2–5,6	5,02		5,02
Гемоглобин, г/л / Hemoglobin, g/L	117–166	151		149
Тромбоциты, $\times10^9$/л / Platelets, $\times10^9$/L	150–400	198,00		289,00
Микроальбумин, мг/л / Microalbumin, mg/L	(0,0–30,0)	500		
Микроальбумин/креатинин, мг/л / Microalbumin to creatinine ratio, mg/L	(0,00–2,50)	71,40		
Фибриноген (Клаусс), г/л / Fibrinogen level (Clauss method), g/L	(2,00–4,00)	5,08	3,16	
Волчаночный антикоагулянт подтв. / Lupus anticoagulant confirmatory test	(0,90–1,20)		0,98	
Холестерин, ммоль/л / Cholesterol, mmol/L	(3,60–5,18)		5,59	6,93
Холестерин ЛПНП, ммоль/л / LDL cholesterol, mmol/L	(0,00–2.60)	4,39		
Альбумин, % / Albumin, %	(55,8–66,1)		48,4	
Альфа 2, % / Alpha-2, %	(7,1–11,8)		18,3	
Альбумин, г/л / Albumin, g/L	(34,80–48,10)		29,04	
Альфа 2, г/л / Alpha-2, g/L	(6,10–8,40)		10,98	
Глюкоза, ммоль/л / Glucose, mmol/L	(3,33–5,55)		7,94	3,86
Антистрептолизин-О, МЕ/мл / Antistreptolysin O titre, IU/mL	(166,00–250,00)		<50	
Мочевая кислота, ммоль/л / Uric acid, mmol/L	(0,21–0,42)		0,53	
IgE общий (R), МЕ/мл / Total IgE (R), IU/mL	(0,00–110,00)		999,95	
Лабораторные показатели мочи / Laboratory parameters of urine				
Белок, г/л / Protein, g/L		6,50	7,60	
Удельный вес, г/мл / Specific gravity, g/mL		1,012	1,017	1,015
Цвет / Color		Светло-желтый / Light yellow	Светло-желтый / Light yellow	Светло-желтый / Light yellow
Эритроциты, кл/мкл / Red blood cells, cells/μL		4,00	10,00	4,00
Цилиндры гиалиновые, кл/мкл / Hyaline casts, cells/μL			3,00	

better intellectual potential, as well as lower mortality (8%). According to the literature, patients with a late-onset form die within 10 years of life [4], however, a patient at the Saint Petersburg State Pediatric Medical University clinic was hospitalized at the age of 17 years 6 months.

The disease is often diagnosed as intrauterine or perinatal viral infections. If intrauterine infection is excluded, it is necessary to diagnose congenital genetic syndromes [4]. Aicardi–Goutières syndrome is manifested by progressive encephalopathy with onset in early childhood, accompanied by hepatosplenomegaly with elevated transaminase levels, thrombocytopenia, basal ganglia calcifications, lymphocytosis, leukodystrophy, increased the level of interferon-α in the cerebrospinal fluid in the absence of data on the presence of a viral infection [4]. Among the hematologic abnormalities in AGS are neutropenia, anemia and thrombocytopenia, severe cases of which were detected with the use

of baricitinib [16]. Patients with AGS have a higher risk of developing autoimmune diseases, including systemic lupus erythematosus [4]. The child in the presented clinical case was admitted with a diagnosis of nephrotic syndrome with diffuse membranous glomerulonephritis. In modern literature, there is a description of kidney damage in Aicardi–Goutières syndrome: in a 19-year-old patient, laboratory analysis showed severe renal failure (creatinine 2.85 mg/dL, GFR 30 ml/min) with arterial hypertension. After 1 month of providing palliative care, he died. Histopathological analysis of the kidney revealed fibrin thrombi and intimal proliferation, signs of thrombotic microangiopathy [18].

Pathogenesis of the disease: interferon-α, the source of which is astrocytes, causes microangiopathy (microinfarcts in the neocortex and cerebellar cortex), calcification of the basal ganglia and perivascular space of small vessels, leukodystrophy (diffuse heterogeneous demyelination with astrocytosis). The basis of such damage is lymphocytic vasculitis with fibrinoid necrosis and microthrombosis. The level of interferon-α in the cerebrospinal fluid increases at the onset of the disease and can normalize during the development and stabilization of the disease, as happened in the patient in the described clinical case.

Diagnosis of this syndrome is difficult, since the onset of the disease and clinical course resemble intrauterine infections, inherited metabolic diseases, epilepsy, so the true prevalence of the disease is unknown. The criteria for the diagnosis of the syndrome are: early appearance of a rash resembling frostbite, the appearance of calcifications in the central nervous system, leukodystrophy, developmental delay, dystonia, positive antinuclear antibody test, increased levels of interferon-α without confirmed infection. Attention is also drawn to patients with systemic lupus erythematosus of atypical manifestations who are not responsive to conventional treatment methods [17]. Long-term dynamic observation, application of neuroimaging techniques and genetic research are necessary [4]. An evaluation of vital organ function is required.

Treatment is symptomatic. The prognosis directly depends on the age of onset of symptoms of the disease, the severity of developmental defects, the severity of clinical symptoms and associated complications [5]. Therapy includes antiepileptic drugs, physical therapy, treatment of concomitant infections, adequate caloric nutrition, endocrinological and ophthalmological monitoring, and prevention of hypothermia. The use of hormonal therapy and high doses of immunoglobulin did not show effectiveness, however, with the administration of corticosteroids, a decrease in the level of interferon-α was noted [4].

CONCLUSION

The discovery of genetic interferonopathies, which include the orphan disease "Aicardi-Goutieres syndrome", on the example of the presented clinical case leads us to understand the systemic effect of interferon overexpression on the body, convinces us of the need for long-term observation of such patients, careful diagnosis of the syndrome and symptomatic treatment, the prognosis of which depends on the age of onset of the disease, its severity and severity of symptoms.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Информированное согласие на публикацию. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

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