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PRACA POGLĄDOWA
REVIEW

Aicardi syndrome – case report and literature review

Zespół Aicardiego – opis przypadku i przegląd piśmiennictwa

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ABSTRACT

Aicardi syndrome (AS) is a rare congenital disorder with neurodevelopmental symptoms that in the significant majority of cases occurs in females. It is typically characterized by a classic triad of symptoms: epileptic spasms, agenesis of the corpus callosum (CC) and central chorioretinal lacunae. It is also necessary to underline that drug resistant epilepsy is the main image of AS. Intellectual disability, ocular, craniofacial and other neurodevelopmental disorders are other common defects found in these patients. This paper presents a patient with AS and refractory epilepsy. She had been treated for epilepsy with epileptic spasms from the age of 3 months, though subsequent medications did not lead to seizure freedom. Further research is needed in order to appropriately address the issue of effective treatment in these patients.

KEYWORDS

drug resistance, epilepsy, Aicardi syndrome, epileptic spasms, chorioretinal lacunae, agenesis of the corpus callosum

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STRESZCZENIE

Zespół Aicardiego (*Aicardi syndrome* – AS) to rzadkie zaburzenie neurorozwojowe, w zdecydowanej większości przypadków występujące u dziewcząt. Zazwyczaj charakteryzuje się klasyczną triadą objawów: napadami zgięciowymi, agenezją ciała modzelowatego i chorioretinalnymi ubytkami w siatkówce. Należy również podkreślić, że padaczka lekooporna jest często głównym objawem klinicznym AS. Ponadto u pacjentów stwierdza się niepełnosprawność intelektualną, zmiany w obrębie narządu wzroku, twarzoczaszki, a także inne zaburzenia neurorozwojowe. W pracy przedstawiono przypadek pacjentki z AS z lekooporną padaczką. Pacjentka jest leczona od 3 miesiąca życia, jednak kolejne modyfikacje farmakoterapii nie doprowadziły do ustąpienia napadów. Istnieje potrzeba prowadzenia dalszych badań, aby właściwie odnieść się do kwestii skutecznego leczenia AS.

SŁOWA KLUCZOWE

lekooporność, padaczka, zespół Aicardiego, napady zgięciowe, ubytki chorioretinalne, agenezja ciała modzelowatego

INTRODUCTION

Aicardi syndrome (AS) is a rare congenital defect syndrome reported in girls and also males with 47, XXY karyotype (with Klinefelter syndrome). A few 46, XY boys have been described to have the characteristic presentation of this syndrome [1,2,3,4,5]. However, mutations in the male population (XY) are almost always lethal [1,6,7]. The main features of this syndrome include epileptic spasms with a tendency of progression, agenesis or hypogenesis of the corpus callosum (CC) and distinctive chorioretinal lacunae. Moreover the presence of all three symptoms is not necessarily needed for diagnosis [1,3,8,9]. Chorioretinal lacunae are defects in photosensitive tissue at the back of the eye [8], which can be confirmed by optical coherence tomography (OCT) [10]. Most pediatric patients with AS develop normally up to the age of 3 months, and then the first symptoms, such as developmental delay and seizures, begin to occur [8]. Optic nerve abnormalities are also characteristic, such as hypoplasia, which in many cases lead to poor vision [9]. Skeletal abnormalities are among the prevalent disorders of AS. Rib and vertebral abnormalities, including scoliosis, are the most frequent problems [1,9]. Characteristic changes in appearance, such as large ears, an inverted tip of the nose and a reduced nasal bridge, occur in patients because of the presence of characteristic craniofacial defects such as a prominent premaxilla and short philtrum [9]. Table I summarizes the clinical manifestation of AS. The etiology of the disease is still unknown; therefore, the diagnosis is mainly based on clinical manifestation [3]. Nowadays we are only able to treat the symptoms [1]. Our case report presents a patient with drug-resistant epilepsy.

Table I. Clinical manifestation of Aicardi syndrome

Type/Localization	Clinical manifestation
Neurological	• Epileptic spasms [1,9] • Agenesis or hypogenesis of corpus callosum [1,9] • Developmental delay [1,8,9] • Microcephaly, axial hypotonia, spastic hemiplegia [1,9] • Polymicrogyria, pachygyria, heterotopia of gray matter [9] • Gross cerebral asymmetry, choroid plexus papillomas [1,9,11] • Intracerebral cysts [1,9,11], ventriculomegaly [1,9,11]
Ophthalmological	• Chorioretinal lacunae [1,9,12] • Hypoplasia of optic nerves (leads to poor vision) [9,12] • Optic nerve colobomas [12] • Pigmentation of optic disc [12,13] • Anomalous retinal vessels, retinal detachment [12,13] • Microphthalmos [12,13], pseudoglioma [12,13] • Macular scars [12,13], iris synechiae and iris coloboma [12,13]
Craniofacial	• Prominent premaxilla and short philtrum (leads to e.g. large ears, inverted tip of nose and reduced nasal bridge) [9]
Skeletal	• Vertebrae and rib defects, scoliosis [1,8,9]
Gastrointestinal	• Feeding problems, diarrhea, constipation, gastroesophageal reflux disease [3,9]
Other	• Small hands (malformations of hands can also occur) [9] • Premature or delayed puberty [9] • Vascular malformations/vascular tumors [9,14] • Skin lesions [9,14], increased incidence of tumors (e.g. choroid plexus papillomas, angiosarcoma) [9,14,15,16]

CASE REPORT

A 15-month-old girl, treated for epileptic seizures from the age of 3 months, with suspected AS, was admitted to the Department of Pediatric Neurology because of an increased number of flexion seizures. The child from an uncomplicated first pregnancy, was born naturally at 40 weeks with a body weight of 4250 g and a head circumference of 36 cm with an Apgar score of 10 points. After the birth, transfontanelle ultrasound revealed agenesis of the CC. The suspected diagnosis of AS was confirmed during ophthalmological examinations, which revealed central chorioretinal atrophic spots. The neurological examination upon admission revealed global hypotonia, a lack of straightening reflexes and significant developmental delay. The seated child sat unsteadily, did not babble, stand or crawl, and could only follow an object with her eyes. In the psychological assessment the girl obtained a score below the first percentile. Magnetic resonance imaging (MRI) of the head revealed a developmental defect of the central nervous system in the form of CC dysgenesis and an abnormal shape of the sulci and gyri in the right frontal lobe (Figure 1–3). The results of the genetic array comparative genomic hybridization (aCGH) test were normal and whole exome sequencing (WES) did not disclose any pathogenic mutations.

At the age of 3 months the girl was hospitalized in the Department of Pediatric Neurology, where the epileptic spasms were diagnosed. Vigabatrin was introduced as the first treatment with a good clinical effect. After about 2 months the girl had a recurrence of seizures. During the therapy valproic acid and clobazam were introduced on an outpatient basis, but they did not yield the expected results. Consequently, after a month of medication, valproic acid was discontinued. Then girl was prescribed vigabatrin in a dose of 100 mg per kg and clobazam in a dose of 1.5 mg per kg. The results of basic laboratory tests were almost in the normal range. Electroencephalogram (EEG) records showed a progression of epilepsy in the form of almost continuous, and continuous generalized synchronous and asynchronous discharges. Nevertheless, there was no correlation between stereotypical facial muscle movements reported by the child's parent during hospitalization or sleep disturbances with the EEG recordings. The repeated head MRI revealed the development of myelination, cortical dysplasia of the right frontal lobe with features of polymicrogyria and a stable CC image. Based on the overall clinical picture of the patient and the performed additional tests, a decision was made to apply two-month adrenocorticotropic hormone (ACTH) therapy and to exclude vigabatrin from therapy. Before introducing the medication the profile of cortisol, glucose, morphology, C-reactive protein (CRP) and ionogram in blood were checked, the results of which were within the reference values. Over the first days of treatment, a similar frequency of symptoms, but with a reduced severity of seizures, was observed. At the end of the first week, complete resolution of epileptic seizures was obtained, which lasted till the end of the child's hospitalization.

The patient was discharged with seizure remission and a recommendation of regular check-ups at the neurological clinic. During the one-year outpatient care, the girl's psychomotor development progressed and no epileptic seizures were observed.

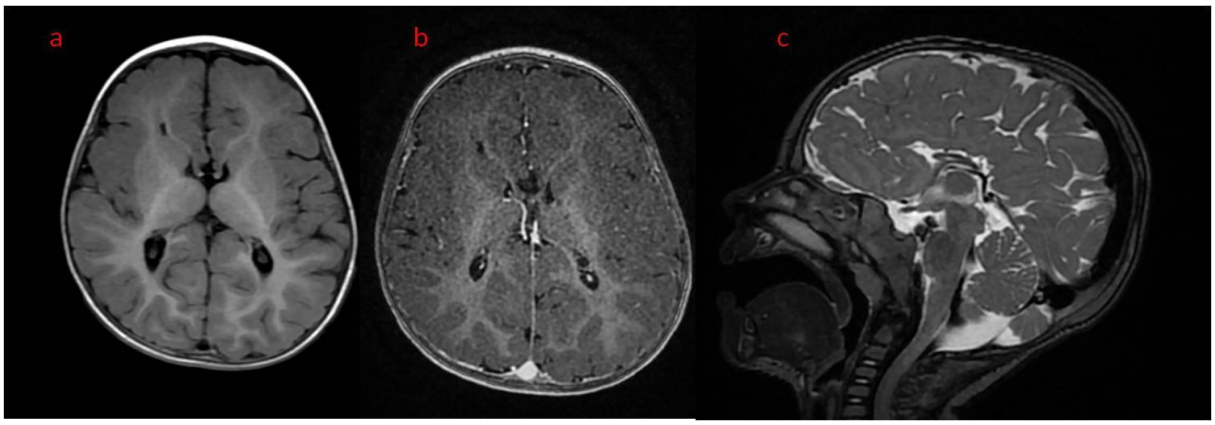

Fig. 1. Magnetic resonance imaging (MRI) of patient at age of 15 months. Axial T1 (a), contrast enhanced T1 (b) and sagittal T2 (c) weighted image showing hypogenesis of corpus callosum (CC). In axial images indirect signs of CC hypoplasia – narrow parallel frontal horns with "racing car" appearance.

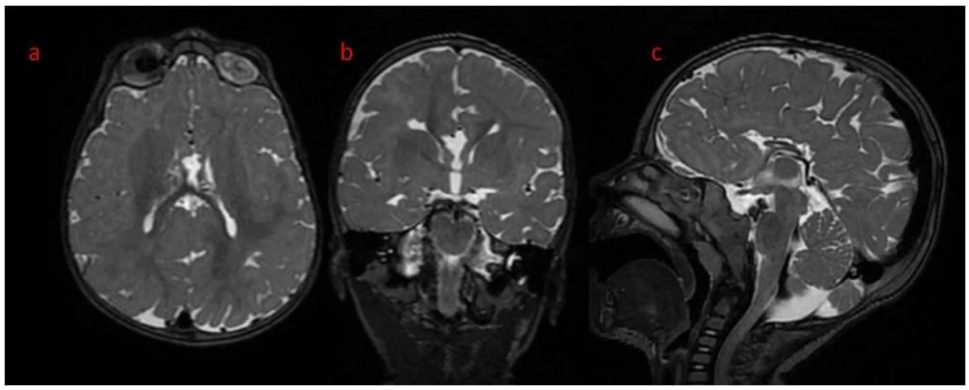

Fig. 2. Magnetic resonance imaging (MRI) of patient at age of 15 months. T2-weighted images in axial (a), coronal (b) and sagittal (c) plane showing hypogenetic corpus callosum (CC), seen only partially in every plane.

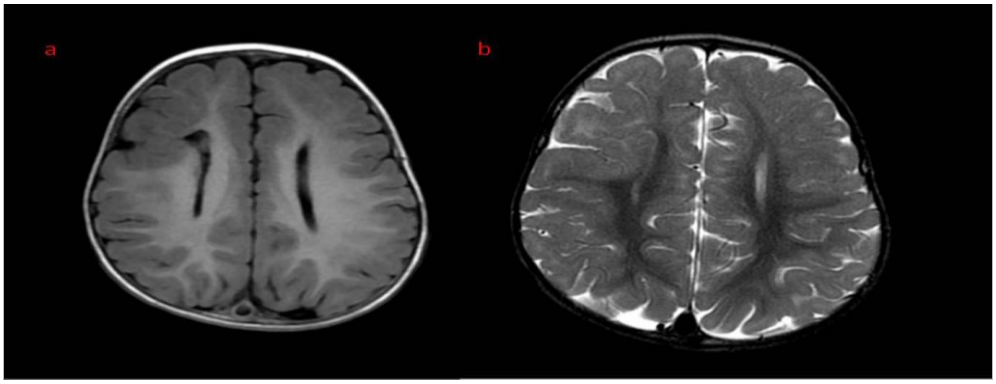

Fig. 3. Magnetic resonance imaging (MRI) of patient at age of 15 months. T1 (a) and T2 (b) -weighted image showing cortical dysplasia of right frontal lobe.

DISCUSSION

The first description of ocular symptoms in an infant with seizures and developmental delay was published in 1946 by Krause [8,17,18]. The French neurologist Dr. Jean Aicardi described the classic elements of the syndrome in 1965. The doctor documented the occurrence of typical symptoms in girls with the absence of CC, abnormal changes in the eye, and epileptic spasms [3,8]. As mentioned above, AS is typically characterized by a classic triad of symptoms throughout the disease but it is not the same in all patients and the triad is not necessary for diagnosis [1]. Optic nerve abnormalities, intellectual disability, scoliosis and other brain malformations are also common defects.

The treatment of AS is strictly symptomatic and aims at controlling seizures, which is difficult to achieve in some cases [2,9]. Synthetic ACTH (Synacthen i.m./i.v.; tetracosactide hexaacetate) is used on a short-term basis to relieve spasms in infants and it seems to show the best clinical results [19]. The response to this treatment varies, and according to studies, is effective in about 50–90% of cases [20]. Some centers prefer to use steroids like prednisolone as the initial medicaments if synthetic ACTH is not available or because of its high cost [21]. The use of high doses of oral steroids is associated with a similar efficacy of about 67%. However, the use of synthetic ACTH improves the treatment outcomes and neurocognitive development. Other drugs that have shown some effectiveness in treating epileptic spasms include vigabatrin, valproic acid, topiramate, nitrazepam and zonisamide [20].

In order to support the main treatment, physiotherapy and other methods are employed to improve the general condition of the patient. To support the development of patients, musculoskeletal support, orthopedic supervision and care of scoliosis should also be carried out [1]. There have been cases of introducing a ketogenic diet [22,23]. The benefits of introducing this diet have been demonstrated in randomized clinical trials, as well as in retrospective and prospective studies [24,25,26]. Vagus nerve stimulation (VNS) is also one of the therapeutic methods, which improved seizure control among a group of patients [23]. Epilepsy surgery seems to be effective in treating seizures, and thus is used in palliative therapy along with stimulation of the vagus nerve [27]. Hemispherectomy, right parietal resection and right frontoparietal lobectomy are a few examples of performed surgeries. Nevertheless, the resection of dysplastic areas in the brain and VNS are difficult to assess resulting from the small number of patients who have undergone these medical treatments [1]. Table II summarizes the current treatments for epileptic seizures/epilepsy in AS.

Aicardi syndrome was suspected in the third month of our patient's life, after which antiepileptic therapy was started. Subsequent medications failed to achieve the desired effect, necessitating multiple changes to the treatment approach. Currently, our patient is being treated only pharmacologically, but owing to the presence of drug-resistant epilepsy, it is possible that in the future she will also be treated surgically. The antiepileptic treatment described in the table is aimed at the treatment of West syndrome as it is the most common type of spasms in patients with AS.

Table II. Currently used methods of treating epileptic spasms and seizures in Aicardi syndrome (AS)

Therapy	Study	Average response
1	2	3
Ketogenic diet	Saito et al. [28]	Partial or transient effectiveness in relieving seizures (4 patients)
	Lund et al. [29]	One patient had no effect, other patients had some seizure control effects (5 patients)
Corpus callosotomy	Saito et al. [28]	Alleviation of seizure severity (1 patient with hypoplasia of corpus callosum)
	Kasasbeh et al. [30]	In first patient, frequency of previously reported seizures decreased since surgery. Second patient developed new focal seizures
	Bernstock et al. [31]	Seizure reduction (> 50%) (1 patient with partial agenesis of corpus callosum)
Left functional hemispherectomy	Saito et al. [28]	Left functional hemispherectomy (performed 5 months later after total callosotomy) resulted in 7-month period without seizures (1 patient)
	Podkorytova et al. [27]	Patient was seizure free for 6 months. Psychomotor development and alertness improved
Vagus nerve stimulator	Kasasbeh et al. [30]	One patient experienced worsening of seizures. Second patient had improvement in seizure control. In third patient no improvement in seizure control was noted
	Lund et al. [29]	One patient had no seizure reduction. Two other patients had slight improvement
	Rosser et al. [23]	Seizure control improvement was noted (5 patients)
Subtotal hemispherectomy	Iimura et al. [22]	Successful reduction in seizure severity (1 patient)
	Rosser et al. [23]	At the time of reporting, patient was seizure free (on one antiepileptic medication)
Multilobar resection	Govil-Dalela et al. [32]	Seizure free for six months (1 patient) There were only 3 severe seizures in 16-month postoperative follow-up
Right parietal resection	Palmér et al. [33]	Seizure free for four years (1 patient)
Right fronto-parietal lobectomy	Podkorytova et al. [27]	Seizure reduction (about 50%) Modest improvement of head and trunk control (1 patient)
Oral prednisolone	Wanigasinghe et al. [34]	Dose: 40–60 mg/day. Cessation of spasms occurred on: day 14 for 28 infants (58.3%), day 28 with electroclinical response being spasm free for 15 infants (31.2%)
	Wanigasinghe et al. [35]	Dose: 40–60 mg/day. Good control of epilepsy after four years: 16 children completely seizure free, 8 children experienced some seizures (75%)
	Gowda et al. [36]	Dose: 4 mg/kg/day (max. dose of 60 mg/day). Cessation of spasms was achieved: on day 14 for 5 children (33.3%), in 3 months for 6 children (40%)
Intramuscular synthetic ACTH	Wanigasinghe et al. [34]	Dose: 40 to 60 IU/day. Cessation of spasms occurred on: day 14 for 18 infants (36.7%), day 28 with electroclinical response being spasm free for 6 infants (12.22%)
	Wanigasinghe et al. [35]	Dose: 40 to 60 IU/day. Good control of epilepsy after four years: 12 children completely seizure free, plus 7 children having some seizures (57.6%)
	Gowda et al. [36]	Dose: 100 IU/day. Cessation of spasms was achieved on day 14 for 9 children (50%), in 3 months 11 children (61.11%, two children died, one of them had AS due to pneumonia)
Monthly pulses of intravenous methylprednisolone (IVMP)	Chatterjee et al. [37]	Good outcomes occurred in 3 months for 19 children (83%), 6 months for 16 children (89%)

cd. tab. II

1	2	3
Hormonal therapy with vigabatrin	O'Callaghan et al. [38]	Dose: prednisolone 10 mg four times a day or intramuscular tetracosactide depot 0.5 mg (40 IU) with vigabatrin 100 mg/kg/day. Cessation of spasms occurred: initially in 133 children (72%), after 13 and 14 days for 166 children (89%), after 42 days for 141 children (76%)
	O'Callaghan et al. [39]	Seizures were absent at 18 months for 126 infants (70.0%)
Hormonal therapy alone	O'Callaghan et al. [38]	Dose: prednisolone 10 mg four times a day or intramuscular tetracosactide depot 0.5 mg (40 IU). Cessation of spasms occurred: initially in 108 (57%), after 13 and 14 days for 132 (69%), after 42 days for 121 children (63%)
	O'Callaghan et al. [39]	Seizures were absent at 18 months for 126 infants (70.8%)

Aicardi syndrome is a genetic disorder reported in the great majority of cases in females [6,23]. There are hypotheses that this disease is caused by a de novo dominant X-linked genetic mutation, and the inactivation of the X chromosome has been correlated with the severity of the phenotype [2,6,23,40]. Nonetheless, several cases of males with the 47, XXY karyotype and some males with the 46, XY karyotype who have a characteristic presentation of this syndrome have been described [2,4,5]. A mutation in a male (XY) whose X chromosome is single and homozygous is almost always lethal [1,6,7]. Some theories say that 46, XY male cases are low-level mosaics for 47, XXY, but this has not been confirmed by research [1,2,3]. Patients with Klinefelter syndrome (47, XXY) have a better chance of survival until birth than patients with a 46, XY karyotype, possibly because they have two X chromosomes [2,6].

The gene responsible for AS has not been identified to date. According to some reports, it is related to an incorrect gene in the Xp22.3 locus [1,41,42,43]. Translocation of the short arm of the X chromosome at this location has been found in several patients with similar clinical symptoms, such as seizures, mental retardation, ophthalmological symptoms and sometimes agenesis of the CC [1,43,44]. The necessity to perform genetic tests during the diagnosis of AS has not been clearly stated. Diagnosis is made on the basis of clinical symptoms and additional examinations. The usefulness of genetic tests is supported by the fact that individual cases of the disease in siblings have been described. This situation has been reported in monozygotic twins, where both girls present all the classic symptoms of the syndrome [1,42]. However, the almost complete absence of family cases suggests the occurrence of a spontaneous mutation in early embryonic development. Such conclusions can be suggested by the analysis of the case of monozygotic twins in which only one of the twins has AS [1,45]. The value of genetic research is also confirmed by the discovery of subsequent mutations that are associated with AS or individual symptoms. Recently, nonsense mutation in *TEAD1* and missense mutation *OCEL1* have been identified. Their presence may suggest that mutations in autosomal genes also contribute to the occurrence of AS [41,46]. Genetic research is very important to understand the etiology of this syndrome and introduce new treatment methods. Nevertheless, the disadvantage of genetic tests is their price and the fact that the benefits for the patient are very small; therefore, they are not routinely performed.

The pathogenesis of AS partially overlaps with other disease entities, and may imitate them in this way or, on the contrary, be misdiagnosed when dealing with another genetic defect or disease. In such cases, differential diagnosis may be necessary. Taking into account the three main symptoms of AS, we can distinguish groups of disease entities with a common symptomatology [3]. Table III encapsulates a succinct summary of the differential diagnosis predicated upon common features. They include genetic defects that involve agenesis of the CC, such as frontal encephalocele, holoprosencephaly, lissencephaly, congenital muscular dystrophy-dystroglycanopathy type A, and Lyon syndrome [47,48,49]. The distinguishing feature of AS is the presence of retinal and ocular abnormalities, which are practically absent in any other syndrome (a retrospective cohort study on 31 children showed that two symptoms and AS were fully consistent with $p < 0.001$) [32]. In AS, the coexisting cysts usually do not connect with the ventricles [9]. Another frequent symptom of AS and other syndromes of inborn errors of metabolism or chromosomal abnormalities is epileptic spasms, which occur as early as around 3 months of age and their patterns develop with age, mainly in the direction of focal seizures [3,9]. The last division can be made on the basis of the presence of ophthalmic abnormalities, where more attention should be paid to details such as the location and nature of changes in the eye, the function of the optic nerve and the coexistence of symptoms from other systems characteristic of other hereditary defects [9]. The gender of the child can also be advised due to the specific way in which the AS is inherited [9]. It is also worth checking if neuronal migration disorders, like polymicrogyria, pachygyria, and heterotopia, are found [9].

Table III. Comparative table of various disease entities with Aicardi syndrome (AS) [3,9,32,47,48,49,50,51]

Disease entities	Common features with AS	Differences with AS
• Frontal encephaloceles • Holoprosencephaly • Lissencephaly • Congenital muscular dystrophy--dystroglycanopathy type A • Lyon syndrome	• Agenesis of corpus callosum (but without isolated cysts)	• No ophthalmic abnormalities • Subependymal heterotopia or polymicrogyria
• Microphthalmia with linear skin defects syndrome	• Agenesis of corpus callosum • Ventriculomegaly • Intracerebral cysts • Seizures • Intellectual disability • Developmental delay • Microphthalmia • Colobomas (iris only) • Other retinal pigmentary defects	• Corneal opacities and cataracts • Retinal and optic-nerve colobomas usually absent • Heterotopia • Epileptic spasms • Vertebral and rib abnormalities
• Focal dermal hypoplasia (Goltz syndrome)	• Agenesis of corpus callosum • Seizures • Microphthalmia • Colobomas and other retinal pigmentary defects • Spine and rib anomalies and facial asymmetry	• Widespread linear skin defects • Adipose tissue herniation • Papillomas of skin or mucous membranes
• Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation • Microcephaly with chorioretinopathy (type I, II and III)	• Mild to moderate developmental delay • Facial deformations • Chorioretinal dysplasia (but is located peripherally)	• Absence of typically normocephalic and neuronal migration defects • Optic nerve colobomas
• Oculocerebrocutaneous syndrome	• Polymicrogyria • Agenesis of corpus callosum • Heterotopia • Microphthalmia	• Orbital cysts • Anophthalmia • Focal skin defects (more common in males than females)
• Orofaciodigital syndrome type IX	• Chorioretinal lacunae • Optic disc coloboma • Developmental delay	• Tongue deformation • Hypertelorism • Telecanthus
• X-linked periventricular heterotopia	• Neuronal migration defects • Seizures • Feeding difficulties and constipation • Heterotopia • Thinning of corpus callosum • Posterior fossa • Cerebellar abnormalities	• No ophthalmic abnormalities
• Tuberous sclerosis complex	• Epileptic spasms • Depigmented areas of the retinal pigment	• Presence of renal cysts • Cortical tubers
• Congenital intrauterine infections (especially toxoplasmosis)	• Epileptic spasms • Microcephaly • Microphthalmia • Chorioretinopathy	• Absence of chorioretinal lacunae and proper development of corpus callosum
• Isolated heterotopia, polymicrogyria or pachygyria	• Heterotopia • Polymicrogyria • Pachygyria	• Lack of other characteristic syndromes

CONCLUSIONS

This case was described by us to emphasize that further work is needed to determine the appropriate treatment. We hope that the treatment described in our case report and its final effects will someday contribute to the creation of effective therapy regimens. It is equally important to include AS in the differential diagnosis. Early detection of the pathology of the CC should prompt the doctor to carry out further tests as a large proportion of AS cases coexist with other defects of the central nervous system.

Author's contribution

Study design – J. Paprocka, M. Machnikowska-Sokołowska, P. Ochman-Pasierbek, P. Olczyk

Data collection – P. Ochman-Pasierbek, P. Olczyk, J. Paprocka, M. Machnikowska-Sokołowska

Manuscript preparation – P. Ochman-Pasierbek, P. Olczyk, A. Doman

Literature research – P. Ochman-Pasierbek, P. Olczyk

Final approval of the version to be published – J. Paprocka, A. Doman, M. Machnikowska-Sokołowska

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