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ALEXANDER DISEASE – ASTROGLIOPATHY CONSIDERED AS LEUKODYSTROPHY – EXPERIENCE OF AN INSTITUTION

CHOROBA ALEXANDRA – ASTROGLIOPATIA UWAŻANA ZA LEUKODYSTROFIĘ – DOŚWIADCZENIA JEDNEGO OŚRODKA

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Abstract

Alexander Disease (ALXDRD) is an autosomal dominant leukodystrophy caused by mutation in one allele of GFAP gene, encoding glial fibrillary acidic protein (GFAP). Most cases occur due to de novo. There are three clinical subtypes of ALXDRD: infantile, juvenile and adult form, but congenital form is also outlined. The disease's spectrum comprises of macrocephaly, progressive pyramidal signs, and seizures in congenital and infantile subtypes. Neuropathologically are enormous number of Rosenthal fibers (RF) mainly around vessels, in subependymal and subpial regions are found. The diagnosis is based on the typical findings on MRI: diffuse white mater lesions with frontal regions preponderance and possibly on the detection of the gene mutation. Here we present six Polish children affected of Alexander disease with congenital (1), infantile (4) and juvenile (1) form. Five of them were previously misdiagnosed as cerebral palsy or unspecific developmental delay; two patients had MRI because of another suspicion, before specific diagnosis was established. Molecular analysis performed in four cases confirmed mutations of GFAP gene; all mutation were de novo. The role of astroglia in brain is shortly reviewed.

Key words: Leukodystrophy, Alexander disease, *GFAP* gene, Rosenthal fibers, MRI

Streszczenie

Choroba Alexandra (ALXDRD) to autosomalna dominująca leukodystrofia spowodowana mutacją w jednym allelu genu GFAP, kodującego kwaśne włókienkowe białko gleju (GFAP – ang. glial fibrillary acidic protein). Wyróżnia się trzy podtypy kliniczne ALXDRD: niemowlęco/dziecięcy, młodzieńczy oraz postać dorosłych, niekiedy wyodrębniana jest postać wrodzona. W obrazie klinicznym obserwuje się wielkogłowie , postępujący zespół piramidowy, a w postaci wrodzonej i dziecięcej - drgawki. W badaniu neuropatologicznym stwierdza się obecność bardzo licznych włókien Rosenthala (RF – ang. Rosenthal fibers), głównie wokół naczyń krwionośnych, podoponowo oraz wokół wodociągu mózgu. Rozpoznanie opiera się obecnie na typowych zmianach w badaniu MR mózgu: rozlanych zmianach w istocie białej mózgu z przewagą zajęcia przednich części półkul. Przedstawiamy przypadki 6. dzieci z postacią wrodzoną (1), dziecięcą (4) i młodzieńczą (1) choroby Alexandra. U pięciorga z nich podejrzewano mózgowe porażenie dziecięce lub niespecyficzne opóźnienie psychoruchowe; dwoje dzieci miało wykonane badanie MR mózgowia z innego powodu, zanim postawiono prawidłową diagnozę ALXDRD. W czterech przypadkach przeprowadzono diagnostykę molekularną wykazując mutację w jednym allelu genu GFAP, były to mutacje de novo. W pracy przedstawiono krótko rolę astrocytów w mózgu.

Słowa kluczowe : Leukodystrofia, Choroba Alexandra, gen *GFAP*, Wókna Rosenthala RM

INTRODUCTION

Alexander Disease (ALXDRD) is an autosomal dominant leukodystrophy caused by mutation in one allele of *GFAP* gene, encoding glial fibrillary acidic protein (GFAP) [OMIM 203450]. Three subtypes of ALXDRD are established: infantile/childhood (42%), juvenile (22%) and adult (33%), but severe neonatal/congenital form is also delineated by some authors [9, 10, 11]. The disease is named after W. S. Alexander who was the first to describe progressive fibrinoid degeneration of fibrillary astrocytes in 16 mo old infant with macrocephaly and mental retardation [1].

The ALXDRD is characterised by macrocephaly and progressive piramidal signs. In infantile/childhood subtype - developmental delay of different degree and seizures are observed. In juvenile form bulbar and pseudobulbar symptoms predominate; at the beginning intellectual function is normal, but over years decline of cognitive function is noted. In adult form ataxia followed by spasticity and sometimes dementia is observed [6, 11]. Characteristic brain MRI pattern includes diffuse white mater lesions with frontal preponderance [12]. Additionally, in more severe cases swelling and hyperintensity or hypointensity of basal ganglia and thalamus on T2- weighted images are observed, rarely shrinking of these structures in late phases of the disease. Focal lesions in cerebellum and brain stem were described in atypical forms [13, 14].

On neuropathologic examination the brain is somewhat enlarged, its weight is abnormally increased and shows enormous number of Rosenthal fibers (RF) mainly around vessels, in supependymal and subpial regions. Paucity of myelin sheets to a variable extent is found in the cerebral, cerebellar and brain stem white matter [4, 5]. Most cases of Alexander disease occur de novo [4,11]. There is no clear genotype-phenotype correlation amongst a type of mutation and severity of the disorder [11].

PATIENTS AND METHODS

We present 6 children (3 boys and 3 girls) of Polish origin born to healthy nonconsanguineous parents. The inclusion criteria in 5 children were brain magnetic resonance imaging (MRI) according to van der Knaap et al: hyperintensity of the white matter in T2 and Flair sequences with frontal preponderance, periventricular rim of decreased signal intensity on T_2-weighted images and elevated signal intensity on T_1-weighted images, abnormalities of the basal ganglia and thalami (elevated or decreased at T2 signal intensity and swelling or atrophy), brain stem abnormalities, contrast enhancement of one or more of the following: ventricular lining, periventricular rim, frontal white matter, optic chiasm, fornix, basal ganglia, thalamus, dentate nucleus, brain stem [12]; in 1 case CT and typical clinical course. MRI was performed on a 1,5T unit apparatus. SE/T1-, FSE, T2-weighted and FLAIR images were obtained in axial, coronal and sagital planes. Clinical ALXDRD phenotypes were established according to international clinical criteria as connatal/neonatal (progressive macrocephaly and developmental delay since birth), infantile (onset below 2 yrs of age) and juvenile (onset between 2-12yrs) [11]. Medical histories and clinical findings were analyzed, including head circumference, height, and weight, onset of clinical signs and symptoms, disease course, presence of mental and motor problems, signs of bulbar dysfunction and epilepsy. Three generation pedigree of all families were analysed. Sequence analysis of the *GFAP* gene of 4 patients was performed at White Matter Diseases Centre Vrije University of Amsterdam as described earlier [12, 13].

RESULTS

Medical history and clinical picture

Case 1. A boy, birth weight 3.500 g, head occipitofrontal circumference (OCF) was 38 cm (97pct). His psychomotor development was severely delayed since birth and rapid head circumference growth was observed during infancy. Decreased muscle tone noted in the first months transformed gradually to tetraparesis with elevated reflexes and opisthotonus. Epileptic seizures of different types occurred. Cerebral palsy due to untreated hydrocephaly was suspected, but brain CT performed at the age of 2 years showed enlarged brain with hypodense frontal white matter lesions (which may correspond to some white abnormalities suggesting leukodystrophy), basal ganglia enlargement and mild supratentorial hydrocephaly probably due to aqueductal stenosis. He died at the age of 6 yrs with severe tetraparesis and cachexy. Parents did not agree to autopsy.

Case 2. A girl, birth weight 2900 g, OCF was 37 cm (90pct). Her psychomotor development was moderately delayed. Clumsiness and frequent falling down were observed. Nonspecific intellectual disability was suspected. At the age of 5 her OCF was 54 cm (>97pct) but her height was 109 cm (10pct). MRI showed widespread white matter lesions mainly in frontal lobes as well as swelling of the basal ganglia with their hypointensity on T2 weighted images. At the age of 6 abnormal limbs movements mainly dystonic and choreo-athethotic appeared. Slowly progressive spasticity of lower limbs developed within the next years. Easy chocking frequently occurred. In her teens slowly progressive intellectual decline and motor disability became evident. Seizures were not observed but abnormal eeg activity was noted. Now, at the age of 23 yrs she presents pyramid-extrapyramidal symptoms and walks with support. Her intellect assessed in International Leiter Performance Scale is 99.

Case 3. A boy, birth weight 3100 g, OCF was 34cm (50pct). His psychomotor development was mildly delayed. At the age of 3yrs gait disturbances and febrile seizures occurred followed over years by epilepsy with rare generalised clonic-tonic attacks. Gradually ataxia and spasticity of lower limbs appeared. Cerebral palsy was diagnosed, but progressive motor dysfunction was observed. At the age of 8 he was 114 cm tall (7 cm<3pct) but his OCF was 55 cm (90 pct). Infrequent seizures were still observed. In his teens progressive intellectual decline and motor disability were observed as well as growth failure, tendency to chocking, vomiting and cachexy. His MRI showed white matter lesion with frontal preponderance. Presently, he is 19yrs old, he walks with support and needs assistance with dressing and feeding.

Case 4. A girl, birth weight 2900 g, OCF was 31 cm (3pct). Her psychomotor development was moderately delayed. She started to walk at the age of 4yrs but her gait was atactic, broad based and deep tendon reflexes were elevated. Progressive four limb spasticity was found mainly in lower limbs. Cerebral palsy was diagnosed although worsening of motor dysfunction was progressive. At the age of 6yrs tonic-clonic seizures appeared and epilepsy was diagnosed. At the age of 8yrs her height was 112 cm (<3pct), her weight was 16,5kg but OCF was 52 cm (50pct). MRI showed white matter changes with frontal predominance. She had a tendency to vomiting and anorexy. Further observation revealed tendency to choking, progressive spasticity, cachexy as well as progressive general motor and mental dysfunctions. Presently she is 18yrs old and walks with support.

Case 5. A boy, birth weight 3100 g, OCF was 33 cm. His psychomotor development was mildly delayed. At the age of 14 months febrile seizures occurred, followed by epileptic attacks repeated every few months. CT scan was performed at the age of 3yrs and suggestion of brain oedema was made because of very narrow ventricles and narrowed pericerebral spaces, but brain MRI revealed lesions of frontal white matter, narrowing of the lateral ventricles and mildly increased volume of the basal ganglia. The next MRI after 2 years showed progression of frontal white matter lesions. Now, at the age of 7yrs, his growth is 110 cm (5 cm<3pct), but his head OCF is 54cm (90pct). Apart of brisk tendon reflexes and mild clumsiness, no abnormalities were detected on neurological examination. His IQ score in Raven scale remains within the normal range.

Case 6. A girl, birth weight 3200 g, OCF was 32 cm. Her psychomotor development was normal. At the age of 6yrs tendency to morning vomitus and transient talking disturbances was noted. Brain tumor was suspected so MRI was performed and showed white matter involvement with frontal predominance and mildly swollen and hyperintense basal ganglia. She was a charming, joyful girl, with weight 110 cm (10pct) and her OCF was 54 cm (97pct). Her intellectual function in WISCR-R was normal IQ =112. Further observation revealed progressive dysphagia and dysarthria, tendency to choking and vomiting as well as gait disturbances - broad based, disturbed by dystonic spasm. Deep tendon reflexes were elevated. At present she is 18, 155 cm tall (3pct), her OCF is 57,5 cm (97pct). Her IQ score in international Leiter scale is 90.

Our patients' clinical features are presented in table I.

MRI and CT data

Characteristic extensive white matter lesions with frontal predominance were present in all cases (fig. 1). Marked enlargement of the brain and mild hydrocephaly in case 1 were detected at CT. In older children subcortical white matter was spared. In case 5 narrowing of pericerebral spaces and lateral ventricles suggested brain oedema. At MRI typical spots at the frontal horns were also. Basal ganglia were shrunken and hyperintense in case 2 and 4, but swollen and hypointenve in cases 1,3,5 and 6. Basal ganglia swelling was associated frequently with narrowing of the lateral ventricles (fig. 2). There were also abnormalities in cerebellar white matter and in the hili of dentate nuclei (fig 3). In case 6 multifocal lesions in medulla oblongata were found (fig. 4).

The data are presented in table II.

Molecular analysis

Molecular analysis was performed only in patients 2,3,4 and 6 and in all of them a heterozygotic mutation in the first exon of *GFAP* gene was detected. There was no DNA sample of patient No 1, but authors decided to include his clinical data because of typical clinical pattern of disease and CT picture (see tab.III). The mutations were not detected in DNA of the parents, confirming that the mutations arose de novo. Patient's No 5 had no molecular confirmation.

DISCUSSION

We present 6 patients with typical forms of Alexander disease (ALXDRD) diagnosed by MRI or CT . The disease is astrogliopathy presenting mainly as leukodystrophy with characteristic neuropathological findings - Rosenthal fibers (RF), but in fact, it is a disorder of all the brain tissues [2]. Astrocytes play a house-keeping functions in the brain - numerous important roles, including structural, metabolic and nutritive ones (glucose reserve buffer and lactic acid provider). They modulate synaptic transmission through secretion and/or absorption of neurotransmitters. They are also involved in the maintenance of the blood–brain barrier and regulation of blood flow by Ca^{+} wave, water-electrolytes balance and maintenance of extracellular environment. They play an important role in the nervous system repair. So, the astrocytes dysfunction results in the dysfunction of the whole brain [7, 8]. GFAPs is a principal intermediate filaments of astroglial cells present mainly in their processes but also in the cytoplasm. Mutations in *GFAP* gene lead to storage of mutated GFAP visible under microscope as Rosenthal fibers (RF) [3]. RF are irregularly shaped eosinophilic structures. They are not specific for ALXDRD but are also detected in chronic infectious processes, multiple sclerosis, amyotrophic lateral sclerosis, neoplastic (low grade astrocytomas) as well as following injuries [5, 7]. RF stovage results of degenerative changes in the cytoplasm and cytoplasmic processes of astroglia and consist of deposits of abnormal GFAP accompanied by ubiquitine, alfa-B-crystallin and HSP27 [8]. It is suspected, that the storage is due to gain of function type mutations of *GFAP* gene, but disturbed turnover of truncated GFAP could not be excluded [6, 8]. In the Alexander disease, RF are scattered in the whole brain but they are the most numerous in the subpial, perivascular and subependymal regions [1, 5]. Macrocephaly observed in ALXDRD is caused to massive storage of abnormal enlarged astrocytes and its processes. The earlier is the onset of the disease the larger is macrocephaly and the brain is heavier. [11]. The storage is also responsible for narrowing of lateral ventricles and pericerebral spaces, swelling of basal ganglia and thalamus which may be misdiagnosed as brain edema on CT as in the case 5. Massive subependymal periaqueductal

Table I. Clinical picture of the presented patients.
Tabela I. Dane kliniczne pacjentów M – płeć męska, F – płeć żeńska.

	Sex ***Płeć***	**Age of onset** ***Poczatek choroby***	**Psychomotor development** ***Rozwój psychoruchowy***	**Seizures** ***Drgawki***	**Macrocephaly** ***Wielkogłowie***	**Clinical course** ***Przebieg kliniczny***	**Vomits** ***Wymioty***	**Choking** ***Krztuszenie***	**Previous diagnosis** ***Uprzednia diagnoza***	**Age now (yrs)** ***Wiek obecnie (lata)***
1	M	Neonatal *Okres noworodkowy*	Severely delayed from beginning *Od poczatku opóźniony*	++	+++ and mild hydrocephaly *Niewielkie wodogłowie*	Severely progressive *Szybko postępujący*	++	++	Neglected hydrocephaly /cerebral palsy *Mózgowe porażenie dziecięce wskutek nieleczonego wodogłowia*	Died at 6 *Zmarł w 6r.ż.*
2	M	<2yrs	Moderately delayed *Umiarkowane opóźnienie*	+	++	Slowly progressive *Wolno postępujący*	+	+	Cerebral palsy *Mózgowe porażenie dziecięce*	19
3	F	1th yr	Moderately delayed *Umiarkowane opóźnienie*	-	++	Slowly progressive *Wolno postępujący*	++	+	Cerebral palsy *Mózgowe porażenie dziecięce*	23
4	F	2yrs	Moderately delayed *Umiarkowane opóźnienie*	+	+ relative *względna*	Slowly progressive *Wolno postępujący*	+++	++	Cerebral palsy *Mózgowe porażenie dziecięce*	18
5	M	5yrs	Normal *prawidłowy*	+	+ relative *względna*	Slowly progressive *Wolno postępujący*		+	Epilepsy *Padaczka*	7
6	F	6yrs	Normal followed by regression *Prawidłowy z nastepowym regresem*	-	+ relative *względna*	Very slowly progressive *Bardzo wolno postępujacy*	+++	++	Susp. brain tumor *Podejrzenie guza mózgu*	18

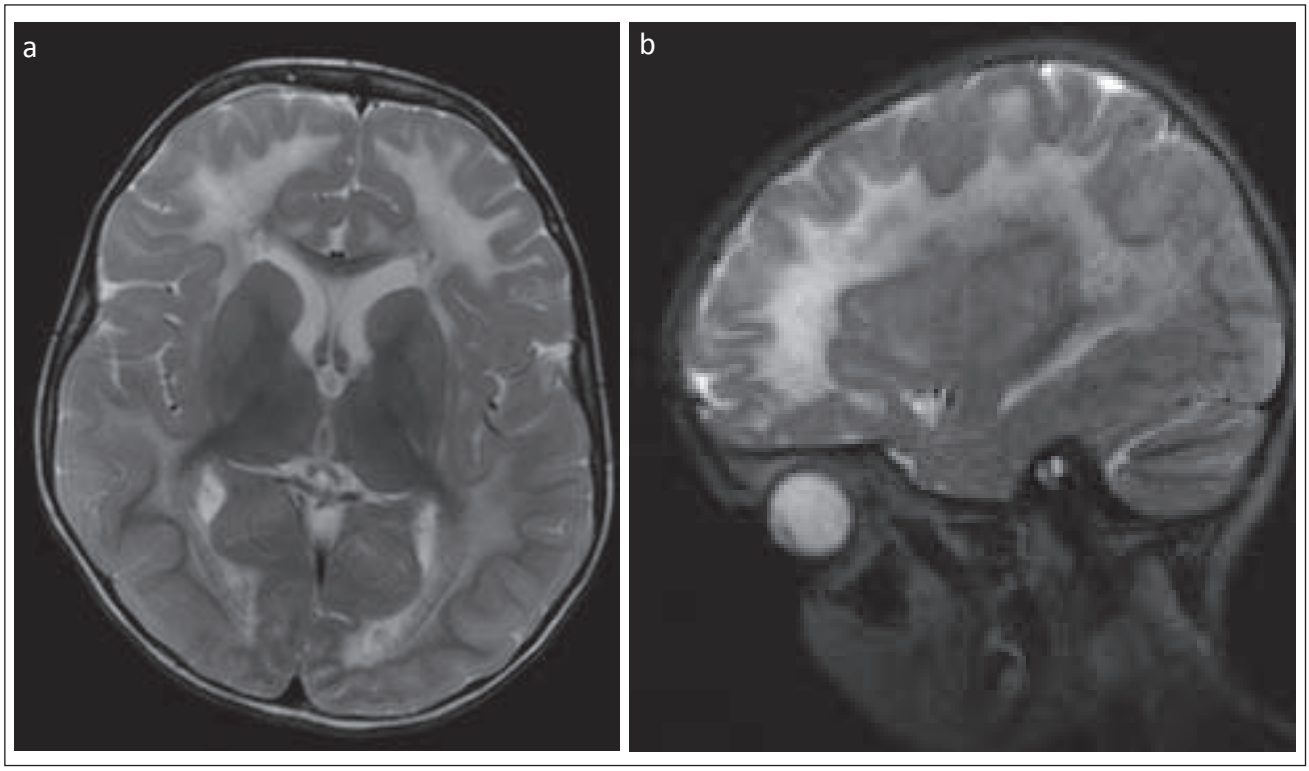

Fig. 1. MRI of patient 3 with infantile/childhood form with more severe clinical course of the disease. Extensive white matter lesions with frontal predominance on T2 sequence, A – axial section, B – sagital section.

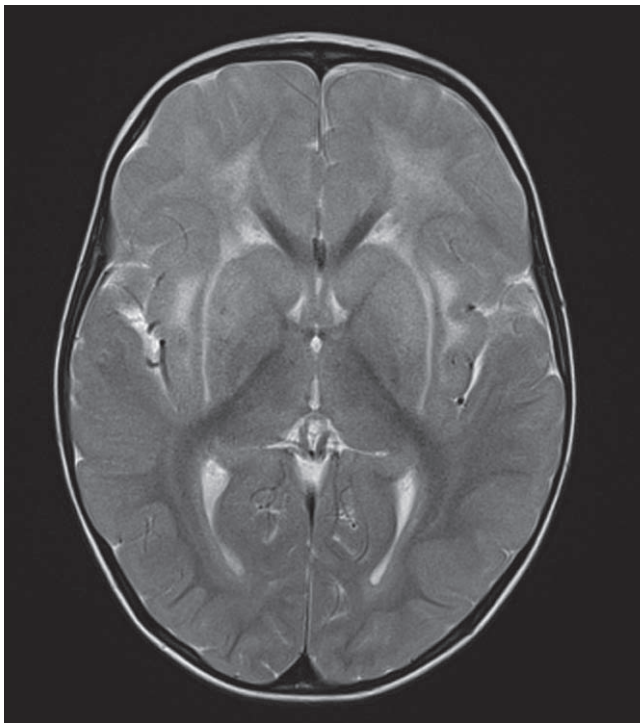

Fig. 2. MRI of patient 5 with infantile/childhood form with milder clinical course of the disease. White matter lesions with frontal predominance on T2 sequence. See also narrowing of the lateral ventricles and pericerebral spaces due to swelling of basal ganglia.

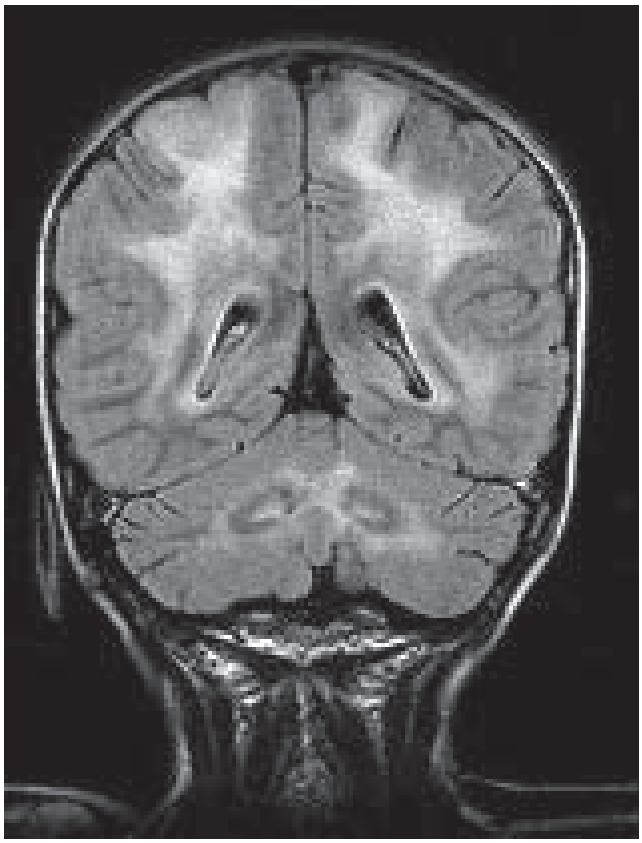

Fig. 3. MRI of patient 6 with juvenile form. lesions in the hili of dentate nucleus and cerebellar white matter apart of cerebral white matter. FLAIR sequence.

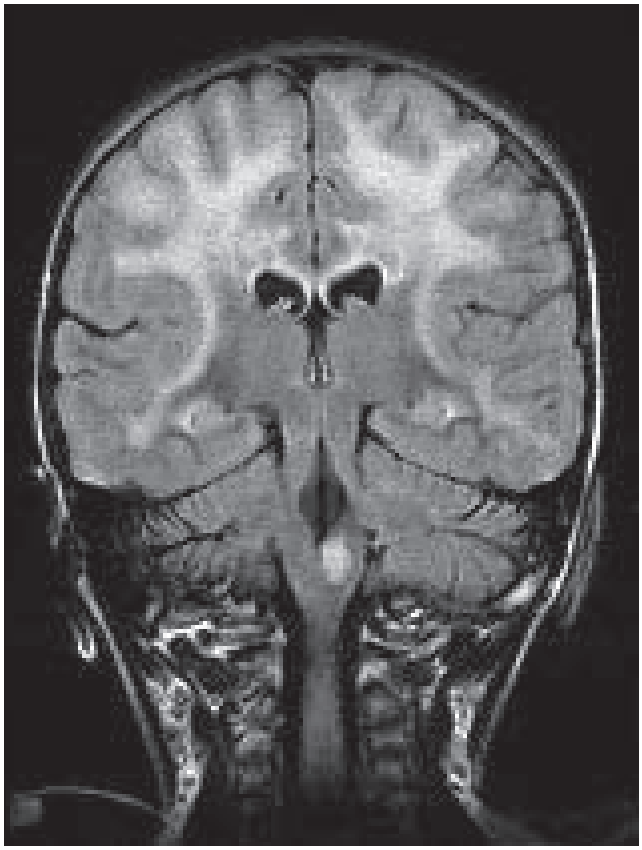

Fig. 4. MRI of patient 6 with juvenile form showed lesion in medulla oblongata apart of cerebral white matter. FLAIR sequence.

deposits of RF in congenital type of ALXDRD may cause hydrocephaly as in case 1 [1, 11]. W.S. Alexander's 16mo patient's brain was "too large and too heavy" - weighted 1210 g (normal – around 1000 g), and lateral ventricles and cavum septi pellucidi were moderately dilated [1, 5]. White matter damage in congenital and infantile type of Alexander disease is of hypomyelinating and dys/demyelinating type, in the remaining forms dys/demyelinating is always present [5]. These pathological changes are responsible for motor dysfunction. Abnormalities of cerebral cortex result in developmental delay or intellectual decline and seizures. Althought ALXDRD is rare, the very characteristic MRI brain picture with extensive cerebral white matter lesions with frontal predominance in classic forms let to prompt the diagnosis [12, 14]. Additional criteria, such as periventricular rim with high signal intensity on T1-weighted images and low signal on T2-weighted images, abnormalities of basal ganglia and thalami, brain stem abnormalities, and contrast enhancement of particular gray and white matter structures are sufficient for an in vivo MR imaging diagnosis. Unusual variants of the disease were also described by MS van der Knaap et al. [13]. Our patients MR and CT imaging pattern were specific for ALXDRD. Case 1 was observed by one of us from the age of 2 in the eighties of XX century when only CT was available. Cases 2-4 were for several years mistaken for cerebral palsy due to near stationary, slowly progressive course of the disease. Delay in specific diagnosis was caused by delayed MRI. In all cases clinical symptoms were qualitatively the same but of different degree even in children with the same mutations. Patients with congenital and infantile forms presented developmental delay and macrocephaly from infancy. After years, pyramidal signs with spasticity appeared. Seizures were also observed but rather not frequently and were easily controlled by antiepileptic therapy. However all the mutations were detected in the first exon of *GFAP* gene somewhat different phenotypes were observed. It might be influenced by different genetic background, epigenetic and environmental factors. In patient with juvenile form psychomotor development was normal and leukodystrophy was detected during diagnostics process of recurrent vomiting, but patients did not present any neurological symptoms. In the case 5. leukodystrophy was unexpectedly detected during diagnostics of recurrent febrile seizures. Because of narrowing of ventricles and pericerebral spaces brain oedema was suspected at CT. Just only MRI showed typical picture of ALXDRD. In case 6 bulbar and pseudobulbar signs appeared (dysphagia, dysarthria) over years but cognitive function was intact up to teens, only then some symptoms of cognitive decline appeared. In all children head circumference was at 97 pct. but growth was deficient (below 3pct.). In differential diagnosis of ALXDRD Canavan disease (CD) must be taken into account. It is characterized by a combination of macrocephaly, extensive cerebral white matter changes but without frontal preponderance and with characteristic NAA (N- acetylaspartic) peak at on MR spectroscopy, followed by urine elevated NAA excretion by GCMS analysis. However, in CD the thalamus and globus pallidus are involved with typical sparing of the putamen and caudate nucleus. Megalencephalic leukoencephalpathy with subcortical cysts (MLC) may be exluded because of widespreed involvement of the whole white matter and cysts in frontal and temporal lobes. Glutaric aciduria type 1 (GA1) which also presents with macrocephaly has different MRI pattern with hypoplasia of temporal lobes, basal ganglia lesions and mild white matter damage and may be detected by elevated excretion glutaric acid in urine [6]. In questionable cases molecular analysis is advisable.

CONCLUSIONS

Alexander disease is a rare astrogliopathy easily diagnosed by MRI as white matter lesions with frontal predominance. The disease confirms the important role of astrocytes in the function of central nervous system. Slowly progressive course may be misleading and cause misdiagnosing it of cerebral palsy but macrocephaly, real or relative to stunted growth, is the characteristic symptom directing to proper diagnosis.

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Table II. MRI/CT data of the patients (nd – no assesed).

Tabela II. Zmiany w MRI/CT pacjentów (na – nie badano).

No	White matter lesions MRI (or CT) *Zmiany w istocie białej*	Periventricular rim *Rąbek okołokomorowy*	Lateral ventricles *Komory boczne*	Basal Ganglia *Zwoje podstawy*	Spots at frontal horns *Punktowate zmiany w rogach przednich*	Medulla oblongata *Rdzeń przedłużony*	Hilus of dentate nucleus *Wnęki jąder zębatych*	Other *Inne*
1	CT –global, mainly frontal leukodystrophy, *Uogólniona leukodystrofia z przewagą zajecia płatów czołowych*	na	Hydrocephaly supratentorial *Miernie powiekszone nadnamiotowo*	Swollen Obrzmiałe	na	na	na	Enlarged brain *Mózg powiększony w całości*
2	Widespread with frontal preponderance *Rozlane z przewagą zajęcia pł. czołowych*	+	Mild widening *Niewielkie powiekszenie*	Shrunken *Obkurczone*	+	+	Yes *Tak*	
3	Widespread with frontal preponderance *Rozlane z przewagą zajęcia pł. czołowych*	+	Mild widening *Niewielkie powiekszenie*	swollen + hypointense	+	+	yes	
4	Widespread with frontal preponderance *Rozlane, przewagą zajecia pł. czolowych*	+	Mild widening Niewielkie powiekszenie	Shrunken *Hyperintense*	+	+	yes	
5	CT – Brain oedema suspected MRI –white matter lesions with frontal preponderance *CT –podejrzenie obrzeku mózgu Hipointensywne, obrzmienie skorup MRI – zmiany w płatach czołowych*	+	Narrowed *Zwężone*	Hypointense and swollen putamina *Hipointensywne, obrzmienie skorup*	+	no	no	U-fibers spared *Oszczędzone U-włókna*
6	White matter lesions with frontal predominance *Leukodystrofia z przewagą zajęcia pł. czolowych*	+		Hypointensive and swollen putamens *Hipointensywne, obrzmienie skorup*	+	+	+	

Table III. Molecular results, Nd – not done.
Tabela III. Badania molekularne, nie badano.

No patients *Nr pacjenta*	GFAP gene type of mutation *Typy mutacji genu GFAP*	DNA	Protein *Białko*	No of exon *Numer exonu*
1	nd (material not available)			
2	Substitution (*substytucja*)	c.235C>T	p.Arg79Cys	exon 1
3	Substitution (*substytucja*)	c.236G>A	p.Arg79His	exon 1
4	Substitution (*substytucja*)	c.236G>A	p.Arg79His	exon 1
5	nd			
6	Substitution (*substytucja*)	c.262C>T	p.Arg88Cys	exon 1

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