Original article

Folia Neuropathologica

Severe encephalopathy with brain atrophy and hypomyelination due to adenylosuccinate lyase deficiency – MRI, clinical, biochemical and neuropathological findings of Polish patients

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Folia Neuropathol 2009; 47 (4): 314-320

Abstract

Adenylosuccinate lyase (ADSL) deficiency is an autosomal recessive disorder caused by mutation in the ADSL gene. The disease was identified in 1984 by Jaeken and van der Berghe as the first inborn defect of purine biosynthesis. Affected children revealed encephalopathy with epilepsy and marked psychomotor retardation. A neurological examination showed hypotonia, followed sometimes after years by spasticity. The diagnosis is based on detection in the urine and CSF succinyladenosine (S-Ado) and succinylaminoimidazole carboxamide ribotide (SAICAr).

We present brain MR examinations of seven patients with ADSL deficiency in the correlation with their clinical findings. In all cases lack of myelination or of delayed myelination of cerebral white matter was seen. Additionally cerebral and cerebellar atrophy was observed. Neuropathological findings revealed damage of all cellular elements of brain tissue and are cause of observed MR changes. Hypo/dysmyelination seemed to be secondary to damage of oligodendroglia and axons of damaged neuronal cells.

Key words: *adenylosuccinate lyase deficiency, purine biosynthesis, hypomyelination, MRI.*

Introduction

Adenylosuccinate lyase (ADSL) deficiency [OMIM 103050] is a rare autosomal recessive disorder caused by the mutations in the *ADSL* gene on 22q13.1 [9]. The disease was identified in 1984 by Jaeken and van der Berghe as the first inborn defect of purine biosynthesis [1,14]. All affected children revealed encephalopathy. They were developmentally retarded and often presented features which are described as autistic [1,9,14]. Neurological examination showed hypotonia, followed sometimes after years by spasticity. Epilepsy was frequently observed [1,2,14].

The diagnosis is based on the detection of two metabolites in body fluid: succinyladenosine (S-Ado) and succinylaminoimidazole carboxamide ribotide

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(SAICAr), which are abnormally elevated in the urine and cerebrospinal fluid (CSF) [1,2,14], but absent in normal conditions. S-Ado/SAICAr ratio differentiates two types of disease: type I with ratio ~1 and type II with ratio 2-4 [2,14].

The pathogenesis is unknown, but the neurotoxicity of SAICAr has been suggested [2,6,13]. The severity of symptoms correlates with the level of residual activity of the enzyme ADSL [13,14].

To date above 60 cases of the disease have been described [8,11,14]. Brain atrophy and hypomyelination were shortly mentioned in previously published papers [6,8,12].

We present MR examinations of seven Polish patients with ADSL deficiency as well as clinical, laboratory and neuropathological findings.

Material and Methods

We examined seven patients (at the age from 2.5 months to 9.5 years of life) from six kindreds with the diagnosis ADSL deficiency. Case 1 and 2 were siblings.

In all patients were performed physical, neurological, electrophysiological and MR examinations; in four of them MR of the brain was performed twice.

Magnetic resonance (MR) imaging was performed using a 1.5T scanner. Axial, sagittal and coronal SE T1- and FSE T2-weighted images, axial FSE Flair was obtained.

ADSL was diagnosed by identification of high amounts of S-Ado and SAICAr in the urine and CSF by HPLC with UV-VIS detector, TLC (separation imidazoles derivatives and colour their Pauly reagent) and 1H NMR spectroscopy methods.

Results

The clinical features and laboratory findings of the patients are summarized in table 1.

A detailed description of the clinical features of the patients was also presented by us in other papers [3,5]. The molecular findings of the patients were presented by Jurecka et all. [4].

In the patients with the most severe form of the disease (No 1,2,3) MR studies were performed at the age of 1 months. Myelination of white matter at the semiovale centre as well as periventricular regions was delayed and the corpus callosum was thin (Figs. 1-3). Abnormally enlarged subarachnoid spaces, mainly around the frontal and temporal lobes were observed (Figs. 2, 3). Sylvian fissures were markedly widened and features of failed operculisation were visible. Lateral ventricles were mildly enlarged.

In the patient No 1 who gradually worsened, a second MR examination was performed a month later, at the age of 2 months, and showed seriously damaged cerebral white matter especially in the posterior part of the hemispheres – in parieto-occipital areas (Fig. 2). A severe progressive cortico-subcortical atrophy with a marked enlargement of lateral ventricles and pericerebral spaces especially around the frontal and temporal lobes was also observed. Abnormal si-

Table I. Clinical features and laboratory findings

Case	Age of onset	Firsts symptoms	Epilepsy	Autistic features	Startle reaction to noise sound	Spasticity	Mental retardation	S-Ado/ SAICAR (in CSF)	Age
1.	2 days	hypotonia. seizures	+				severe	0.92	†2.5 mo.
2.	3 weeks	hypotonia, Seizures,	+	+	+		severe	1.12	9 mo.
3.	3 weeks	hypotonia, seizures	+ (periodically drug resistant)	+	+		severe	1.07	11 mo.
4.	4 days	hypotonia, seizures	+ (drug resistant)	+	+	+	severe	nd	4 y.
5.	1 month	hypotonia	+ (periodically drug resistant)	+		+	severe	0.97	8.5 y.
6.	3 months	hypotonia	+	±	+		moderate	nd	4.5 y.
7.	2 months	hypotonia		±			moderate	nd	3.5 y.

† – *death; nd – not done in CSF (diagnosed in the urine).*

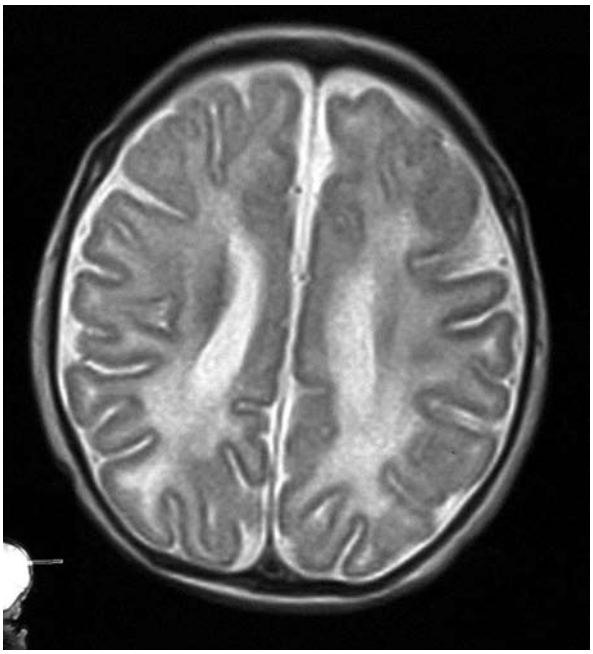

Fig. 1. Case 1, at the age of 1 month. Abnormal signal of cerebral white matter more pronounced in parieto-occipital lobes (T2WI).

gnal of dentate nucleus was also seen (Fig. 3). The child died two weeks later at the age of 2,5 months.

The neuropathological examination of this case showed microcystic encephalopathy with damage of all morphological elements of the brain tissue (neuronal cells and their processes, astroglial cells, oligodendroglial cells, myelin sheets as well as small vessels) The myelination was normal for age in the structures in which myelination begins in the late gestational period. However, the myelin showed severe damage with marked reaction of hypertrophic astroglial cells which also revealed severe signs of destruction (Fig. 4).

Patients No 2 and 3 had a multitude of polymorphic epileptic seizures, which at the beginning were difficult to treat, but after several weeks they gradually improved. The next MRI of the brain, at the age of 9 and 11 months respectively, showed further progressive cerebral and cerebellar atrophy (Fig. 5). Hypomyelination of white matter was still observed especially in periventricular regions, but some progress in myelination was seen. The white matter volume was reduced and the corpus callosum was very thin. In case 2 abnormal signal of the dentate nucleus was seen.

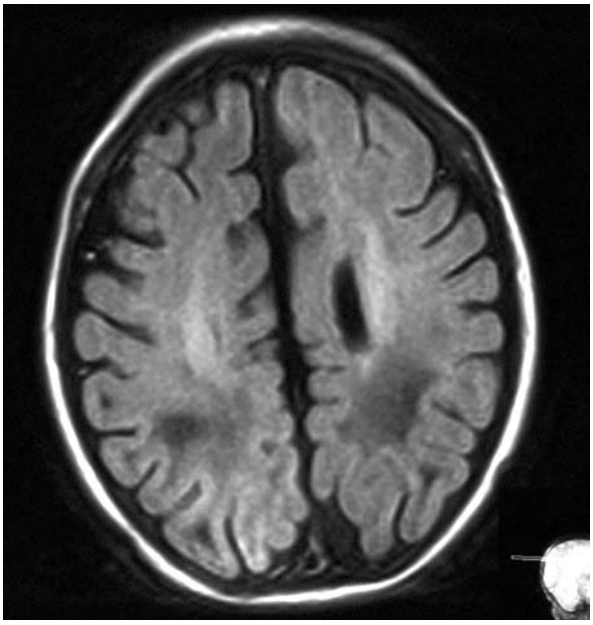

Fig. 2. Case 1, at the age of 2 months. Increasing abnormality of signal of cerebral white matter most pronounced in parieto-occipital lobes as well as brain atrophy (FSE Flair, axial plane).

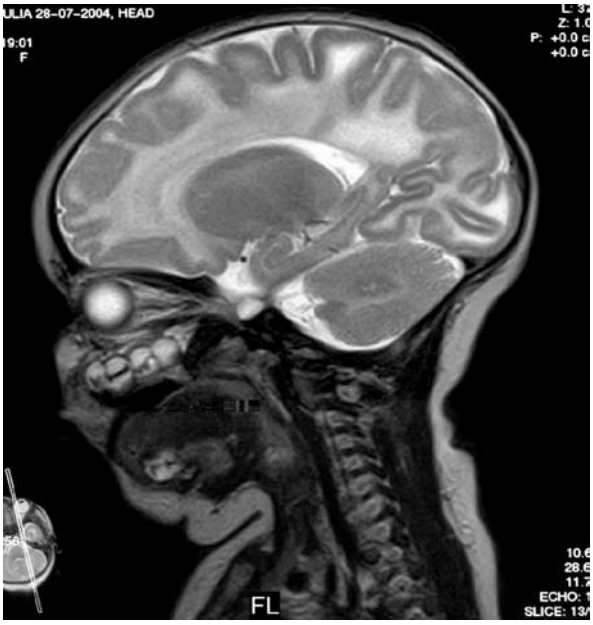

Fig. 3. Case 1. at the age of 2 months. Hypeintense signal of cerebral and cerebellar white matter as well as abnormal signal of dentate nucleus (T2WI sagittal plane).

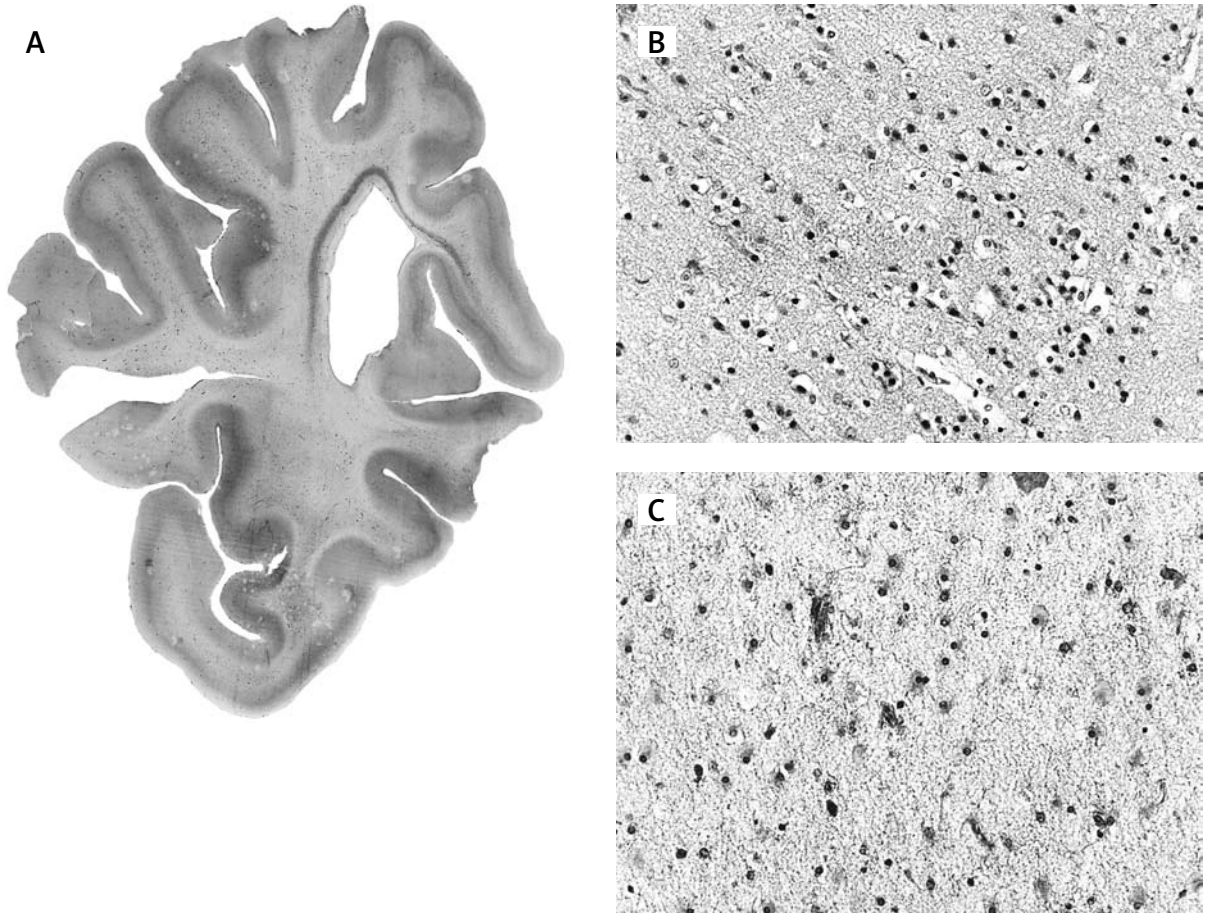

Fig. 4A-C. A. Case 1. Parieto-occipital level of the cerebral hemisphere. Lack of myelin with scanty myelination of visual radiation. Klüver-Barrera. Glass magnification. B. Cerebral cortex with damage and loss of neurons and severe spongiosis of neuropile. H-E, ×200. C. Cerebral white matter with spongiosis, scanty astroglia and oligodendroglia. H-E, ×200.

In patients No 4 and 5 at the age of 4 years – cortico-subcortical atrophy was prominent; especially the volume of hypomyelinated white matter was decreased. The corpus callosum was thin. The lateral ventricles were markedly widened, but subarachnoid space and lateral fissures were only mildly enlarged. In case No 5 an abnormal signal of the posterior part of the basal ganglia was seen (Fig. 6). Cerebellar atrophy was also observed (Fig. 7) as well as abnormal signal of dentate nucleus.

In patients No 6 and 7 with a milder form of ADSL, MR examinations were performed at the age of 1,5 year and 2,5 years respectively. Hypomyelination of the cerebral white matter especially in periventricular areas was seen. Cortico-subcortical atrophy mainly of frontal and temporal lobes was visible. Sylvian fissures were widened. Lateral ventricles were mildly enlarged.

MR of the brain findings are summarized in the table No 2

Discussion

Clinicists are still confronted with difficulties in establishing the proper diagnosis in the patients with encephalopathy of unknown origin, especially with hypomyelination. ADSL deficiency is one of the diseases in which hypomyelination apart of the cortico-subcortical atrophy is a constant findings.

Our observation confirmed that the ASLD deficiency is the disorder seriously destroying the brain. Five out of seven of the patients showed type I of the disease with the same clinical features as was described by others authors [1,2,8,13], two of them presented type II. All of the patients had hypotonia

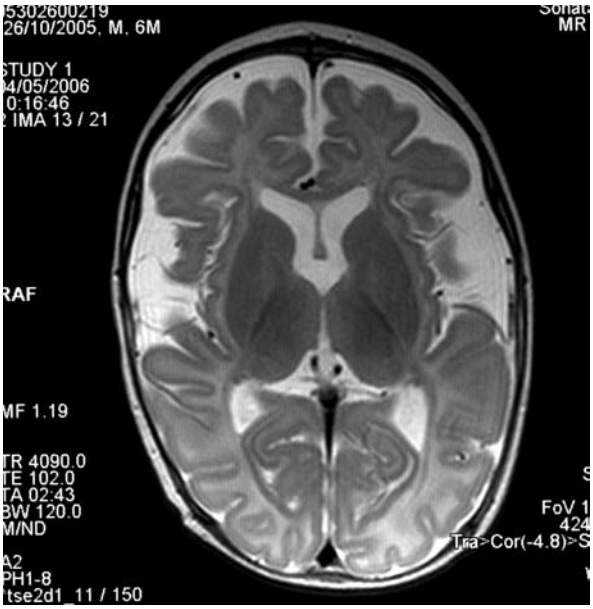

Fig. 5. Case 3, at the age of 7 months. Cortico-subcortical atrophy with enlargement of subarachnoid spacies and widening of lateral ventricles and failed operculisation with enlarged lateral fissure. Abnormal signal of cerebral white mattter (T2WI axial plane).

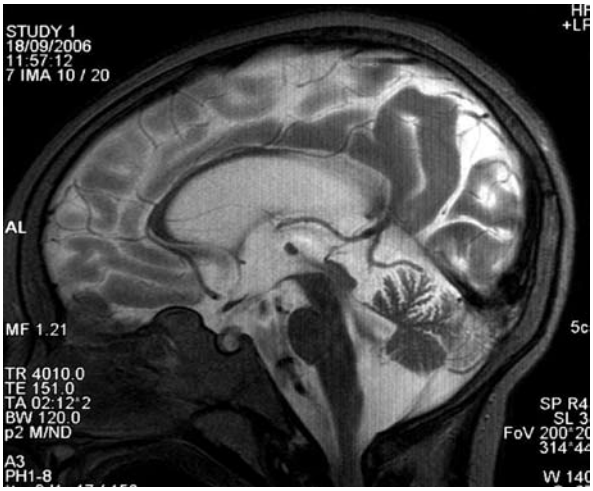

Fig. 7. Case 5, at the age of 5. Atrophy of cerebellar vermis. Thin corpus callosum (T2WI sagital plane).

of muscles from the birth followed after years by spasticity in type I of the disease. One of them (case 1) presented severe fatal variant of the disease but the patient can not be clasified as postnatal fatal pre-

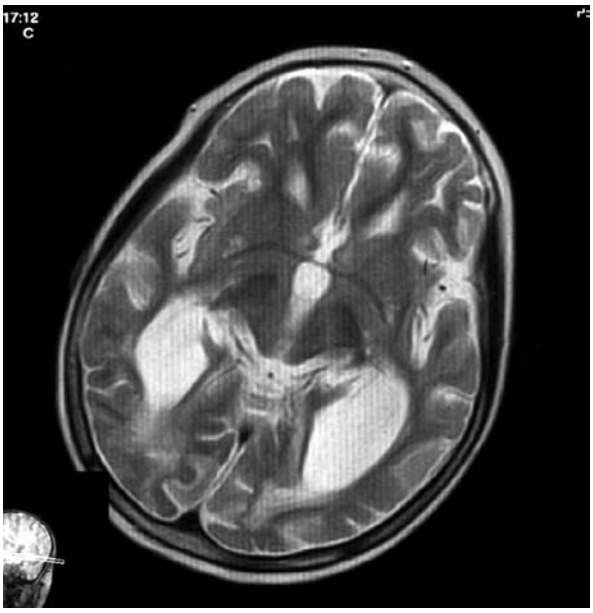

Fig. 6. Case 5, at the age of 5 years. Abnormal signal of posterior part of basal ganglia (T2WI axial plane).

sentation of ADSL deficiency according to criteria established by Mouchegh and other [11]. She was born at term in good condition, with good birth weight and normal head circumference.

All of the patients had MR examinations of the brain during diagnostics procedures of encephalopathy of unknown origin, before the diagnosis of ADSL deficiency was biochemically confirmed. In all of them marked hypomelination of cerebral white matter was described as a main finding. In the first presented child we supposed at first a severe form of vanishing white matter, because at the subsequent MR examination the cerebral white matter was more destroyed than at the previous [5]. It was just biochemical confirmation of SAICAr in urine that let us to establish the proper diagnosis.

Neuropathological diagnosis showed the microcystic encephalopathy with severe damage of all morphological elements of the brain tissue which explains cortico-subcortical atrophy as well as hypo/dysmyelination [10]. The same description was shortly mentioned by others [11]. According to the neuropathological findings it seemed to us that hypomyelination/dysmyelination is probably secondary phenomenon to destruction of neurons and their axons as well as damage of the oligodendroglial cells.

Table II. The results of brain MRI

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Diffuse white matter abnormalities in T2	+++	+++	+++	+++	+++	++	++
Thin corpus callosum	+++	+++	+++	+++	++	++	++
Enlargement of subarachnoid spaces	+++	+++	+++	+++	+	+	+
Enlargement of lateral ventricles	+++	+++	+++	+++	+++	++	++
Widening of Sylvian fissure	+++	+++	+++	++	+	+	+
Abnormal signal of dentate nucleus	+	+	-	-	+	-	-
Abnormal signal of thalamus	-	-	-	+	-	-	-
Abnormal signal of basal ganglia	+	-	-	-	+	-	-
Atrophy of cerebellum	+/-	-	-	++	++	-	-
Atrophy of cerebral and cerebellar cortex	+++	++	++	++	+++	+	+

Mild +, moderate ++, marked +++.

We have to notice that in MRI examinations were visible not only white matter changes but also cerebral and cerebellar cortex atrophy, abnormal signal of subcortical nuclei and thinning of brain stem. Involvement of the basal ganglia and dentate nuclei were mainly observed in the most severe case (No 1) and in the case with the longest duration of the disease (No 5). These structures are especially vulnerable to energy depletion caused by hypoxia-ischaemia, toxic substances and/or other metabolic derrangements. It seemed to us that biochemical disorders connected with ADSL deficiency might be causative factors.

Because the microcystic encephalopathy is also observed in other disorders [7] we suggest that the neurotoxicity of SAICAr is not the only pathogenetic factor, but the changes are the results of combined biochemical disorders. We suppose that one of them could be disorders of energy metabolism, as we concluded from the observation of children whose makedly worsened during energy consumming episodes as febrile infections and/or stress. Until today, the quantitative deficiency of purine nucleotides in the disease was not proven in ADSL deficiency. However, subtle deficite of purine nucleotides and adenylate cyclase which are important for transduction of cellular signaling and activition of many enzymes may play a role in pathology of the disease. Futher examination is necessary to explain the problem.

In conclusion, in every case of progressive encephalopathy with hypomyelination or dysmyelination accompanied by cerebral and cerebellar atrophy should be performed examination for SAICAr and S-Ado in urine and CSF.

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