

Leukoencephalopathy with vanishing white matter due to homozygous *EIF2B2* gene mutation. First Polish cases

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Abstract

Leukoencephalopathy with vanishing white matter (VWM), also called childhood ataxia with central nervous system hypomyelination (CACH), is an autosomal recessive disease caused by mutations in any of the five genes encoding subunits of the eukaryotic translation initiation factor eIF2B.

Neuropathological findings comprise a severe, cavitating orthochromatic leukodystrophy with only small amounts of myelin breakdown products, and predominantly involving the cerebral hemispheric white matter. Within the white matter abnormal oligodendroglial cells are present with abundant "foamy" cytoplasm. In some regions oligodendroglial cells are increased in numbers.

We present three sisters, 18, 11 and 8 years old, with the early to late childhood phenotype. The first signs of the disease were gait disturbances at 4, 2 and 6 years of age, respectively. Neurological examination showed mild tremor of hands and head, truncal ataxia, dysarthria, and hypotonia, after several years followed by spasticity. The course of the disease was slowly progressive. Intellectual abilities are relatively spared.

The MRI showed diffusely abnormal white matter of the cerebral hemispheres. The FLAIR images revealed rarefaction of the affected white matter with some stripe-like structures, suggesting the presence of remaining tissue strands. The abnormalities were most pronounced with the middle sister, who had the earliest onset of the disease.

*A homozygous point mutation in the *EIF2B2* gene was found, 638A>G. Both the parents were found to be carriers of this mutation.*

This is the first description of a Polish family with VWM.

Key words: *Vanishing White Matter Leukoencephalopathy, CACH, orthochromatic leukodystrophy, eukaryotic translation initiation factor 2B-eIF2B*

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Introduction

Leukoencephalopathy with vanishing white matter (VWM), OMIM 603896, was described in the nineties by several centers [4,10,12]. Van der Knaap et al. [12] proposed the name vanishing white matter disease, whereas Schiffmann et al. [10] used the term childhood ataxia with central nervous system hypomyelination (CACH).

The disease is inherited in autosomal recessive manner and caused by mutations in any of the five genes encoding the five subunits of the eukaryotic translation initiation factor eIF2B [6,13,14].

A wide spectrum of phenotypes has been described for VWM/CACH [1,3,9] – from prenatal/perinatal to adult onset. In early-onset forms the course is rapidly progressive with death after several months. In the later-onset forms the course is milder and frequently slowly progressive [1].

In the childhood or juvenile form, the psychomotor development of affected children is usually normal or mildly delayed. The first signs are often gait disturbances. Gradually, truncal ataxia, dysarthria and hypotonia develop. Spasticity is of variable severity. Optic atrophy may develop but it is a rather late sign. Seizures are rare. Intellectual abilities are relatively spared.

Brain MRI shows symmetrical, diffuse white matter abnormalities. Proton density and FLAIR images show that the abnormal white matter gradually develops the same signal intensity as CSF [1].

Neuropathological findings comprise a severe, cavitating, orthochromatic leukodystrophy with only small amounts of myelin breakdown products, predominantly involving the cerebral hemispheric white matter. The U-fibers, internal capsule, corpus callosum, anterior commissure and cerebellar white matter are relatively spared. In the white matter, an increased number of cells is often noted with the morphological features of oligodendrocytes, some of them with abundant and foamy cytoplasm [8,15]. Hypertrophic and occasionally atypical astrocytes are also noted.

Patients and methods

The patients are three sisters (aged 18, 11 and 8 years) from the Polish Highlander's families. The parents were healthy and not known to be consanguineous, although they originated from small, neighbouring villages. There are two healthy brothers.

Neurological examination and electrophysiological studies (EMG, NCV, EEG) were performed.

MRI examinations were performed using a 1.5 T scanner (Edge, Picker), as previously described [5].

DNA analysis: the entire coding sequence of the *EIF2B2* gene (14q24) was analyzed by amplification of all exons including splice donor and acceptor sites by PCR, followed by SSCP and direct DNA sequencing of aberrant fragments (VUMC, Amsterdam).

Case reports

The patients were born after uneventful pregnancies and deliveries. Their birth weight was 3100 g, 3250 g, and 3400 g respectively; their Apgar scores were optimal.

Their psychomotor development was within normal limits, but somewhat slower than that of their healthy brothers. At the ages of 4, 2 and 6, respectively, gait disturbances appeared followed by mild tremor of hands as well as of tremor of the head in the middle sister. Neurological examination at the beginnings of the disease revealed hypotonia, mild ataxia, dysarthria and brisk tendon reflexes. The sisters were able to walk independently for several years. They had no seizures. Brain MRI shows bilateral diffuse cerebral white matter changes. The EEG of the patients showed mild general abnormalities. Brain stem auditory evoked potentials were abnormal as well as somatosensory and visual evoked potentials. Nerve conductive velocities were normal in all sisters.

Routine blood and urine examinations were normal. The lysosomal storage diseases, Canavan disease, peroxisomal defects and mitochondrial disorders were excluded. Muscle biopsy was performed in the middle sister and revealed only nonspecific changes - a different size of muscle fibers and slight lipid accumulation in some fibres; activity of OXFOS enzymes in muscle was normal.

The course of the disease was slowly progressive with episodes of deterioration after febrile infections. The sisters were examined in our department at the ages of 17, 10 and 7 years, respectively.

1. The oldest girl at age 17 had dysarthria, ataxia, mild tremor of the hands and mild spasticity, mainly of the legs. Tendon reflexes were brisk. She was able to walk with support. Fundoscopic examination showed pale optic disks. Her IQ was 73, but the low IQ was partially explained by her poor motor performance. She had a primary

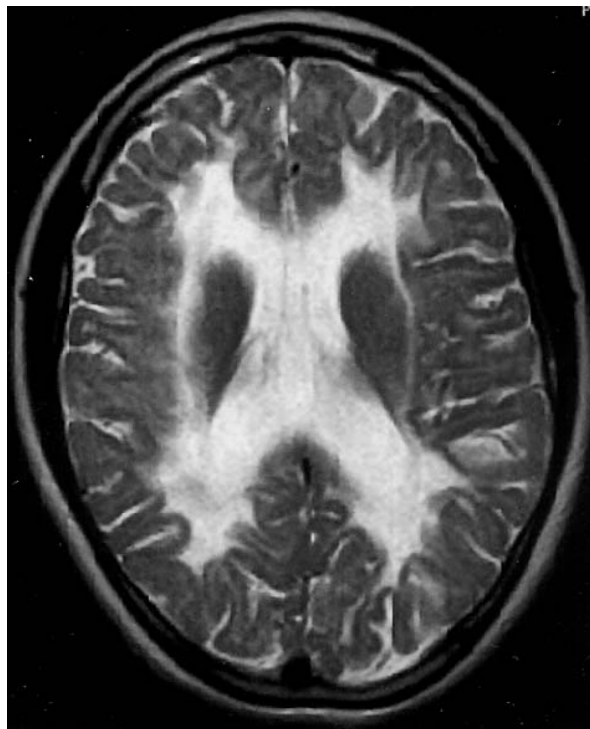


Fig. 1. MRI of the brain of the middle sister (T2 weighted). Bilateral changes in the white matter of both cerebral hemispheres

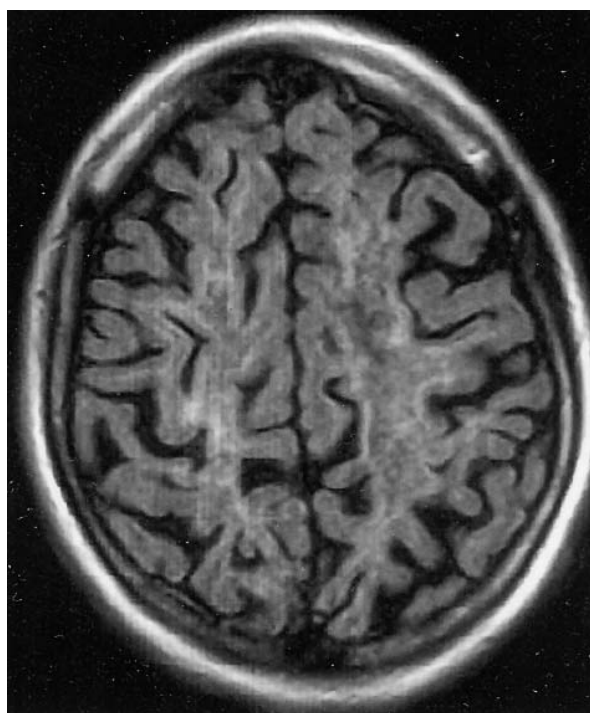


Fig. 2. MRI of the brain (FLAIR). Dotted pattern of the centrum semiovale

amenorrhoea. There were no signs of a thelarche, but signs of an adrenarche were present. Gonadotrophin levels were high (FSH - 150 IU/l, LH - 31 IU/l), while estrogen and progesterone levels were low (oestradiol - 26 pg/ml, progesterone - 0.4 ng/ml) indicative of ovarian insufficiency.

2. The middle sister at age 10 had a marked cerebellar ataxia, serious dysarthria (only the family members could understand her speech), head tremor and spastic tetraparesis. Tendon reflexes were elevated. She was unable to write because of a severe hand tremor. She lost walking without support at age 9 and was wheelchair bound. Ophthalmologic examination showed pale optic disks suggesting optic atrophy. Her IQ was 54.
3. The youngest sister aged 7 displayed only mild ataxia and hypotonia. The tendon reflexes were brisk. She walked without support, but her gait was mildly ataxic. Fundoscopic examination was normal. Her IQ was 81, mainly because of her poor fine motor performance.

Magnetic resonance images and spectroscopy

MRI of the brain of the patients showed diffuse cerebral white matter abnormalities (for detailed description see also [5]). Affected regions were hypointense on T1-weighted and hyperintense on T2-weighted images. The white matter was slightly atrophic with prominent lateral ventricles and subarachnoid spaces. The FLAIR images showed evidence of rarefaction of the white matter with some stripe-like structures suggestive of remaining tissue strands.

The degree of the changes was most severe in the middle sister in whom onset of the disease was earliest.

Molecular investigations

DNA analysis revealed in all three patients a homozygous point mutation in the *EIF2B2* gene, 638A→G, which leads to an amino acid substitution in protein E213G. The parents were found to be carriers of the same mutation.

Discussion

During the last decade several “new” diseases affecting white matter were identified. VWM/CACH was one of them. The causative genes were

identified in 2001 and 2002: *EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4* and *EIF2B5*, encoding the alpha, beta, gamma, delta and epsilon subunits of translation initiation factor eIF2B, respectively [6,13].

The diagnosis of VWM/CACH can be established on the base of clinical features and characteristic MRI findings, indicative of progressive vanishing of the affected cerebral white matter. On CT scans the white matter is very hypodense, almost black. That is why Hanefeld, in a personal communication, referred to the disorder as “black matter disease”. Molecular investigations and identification of mutations in one of the five genes mentioned above confirm the diagnosis and allows genetic counselling and prenatal testing.

To the best of our knowledge about 14% of patients affected by VWM have mutations in *EIF2B2* gene on 14q24 [10]. Homozygous mutation 638A>G which was detected in siblings, has been also found in many other cases [2,10]. This missense mutation is localized in the 5th exon of *EIF2B2* gene and is the second of the most frequently detected pathogenic VWM mutation (6% of all affected patients) [10]. It has been often associated with milder phenotypes [2,10].

Until now, there has been no good genotype-phenotype correlation in VWM/CACH [1,2,3,9,14]. Severity of the disease seems to correlate with age of the onset. The phenotypic variation may in part be caused by the influence of as yet unknown modifying genes or environmental events. The role of intercurrent infections and head trauma causing deterioration has been stressed [3,7]. The mother of the present patients observed severe deterioration after influenza with high fever in her second daughter.

Our patients are an example of phenotypic variation of the disease within one family. Whereas they are homozygous for the same mutation, they present with two different phenotypes. The middle girl has an early-childhood form and two remaining girls have a late childhood form. The course of the disease, as it was described by other authors, is slowly progressive and is more severe with an earlier onset. The 638A>G mutation in *EIF2B2*, leading to a substitution of glutamic acid by glycine in the β -subunit of eIF2B2, causes in most cases a relatively mild form of the disease.

It is interesting that the oldest girl has signs and symptoms of ovarian insufficiency, as it was described before in patients with mutations in the eIF2B genes under the heading of ovarioleukodystrophy [14].

We would like to encourage others to retrospective examination of cases previously diagnosed as

leukodystrophy of unknown origin [11]. The verification is not only interesting but also very important because to the families at risk genetic counseling and prenatal testing may be offered.

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