

# ATYPICAL PRESENTATION OF VANISHING WHITE MATTER DISEASE

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Leukoencephalopathy with vanishing white matter (VWM) has also been called childhood ataxia with central hypomyelination (CACH)<sup>1</sup>. VWM was described by van der Knaap et al.<sup>2</sup> in nine children with a leukoencephalopathy of similar type according to clinical and MRI findings. The onset of the disease was in childhood and the disease course was chronic-progressive with additional episodes of rapid deterioration. The MRI showed diffuse and bilateral leukoencephalopathy with areas that displayed a signal intensity close to that of cerebrospinal fluid (CSF) on different pulse sequences. As the disease progressed white matter rarefaction and cystic degeneration increased. VWM is a disease with an autosomal recessive mode of inheritance. It is related to defects in translation initiation factor eIF2B<sup>3,4</sup>. eIF2B consists of 5 non identical subunits. Clinically the disease is characterized mainly by cerebellar ataxia, usually less prominent spasticity, relatively mild mental decline, and no or mild epilepsy. Optic atrophy may develop, but is not obligatory<sup>2</sup>. Episodes of minor head trauma, febrile infections or fright can result in worsening of the symptoms with subsequent partial recovery<sup>2,4-7</sup>. The deterioration is often accompanied by lethargy and may result in unexplained coma<sup>2</sup>. Most patients die after 2–5 years of disease evolution<sup>5</sup>. Nowadays, it is known that the diagnostics based on the clinical aspects is not always easy. The onset of the disease can be at any age, from antenatal to adult onset<sup>2,5,8-11</sup>. The evolution may be rapid or prolonged<sup>3</sup>. Death may occur soon or after decades<sup>5,8</sup>. Other organs than the nervous system may be affected, especially in early onset<sup>8,12</sup>. There may be unexpected neurological manifestations such as periodic hemiparesis<sup>13</sup>. Beside the different phenotypes, another situation that could lead to a mistake or delay in the diagnosis is the dissociation between the clinical findings and MR images on which the abnormality of the white matter may appear before the clinical phenomena<sup>2</sup>.

So VWM is a disease that presents with different phenotypes and the diagnosis is not always easy. With more universal access to the MRI, the diagnosis should be considered more often. The diagnosis is confirmed by genetic testing, which allows a better definition of the clinical profile of this disease.

## CASE

A boy, 8 years and 10 months old, felt dizziness in June 2006. CT scan revealed bilateral and diffuse brain hypodensity. Soon after, a MRI was performed suggesting a leukodystrophy. He was sent for neurological investigation and was seen on the 31<sup>st</sup> of August, 2006. At that time, he had no complaints.

The pregnancy was complicated due to a disease in his mother (kidney tumor). A caesarean section was performed at term and the baby was healthy. There was a normal psychomotor development and satisfactory progress at school with normal behavior. He had a good general health. He had an older sister, who was healthy. There was no consanguinity in the family. There was a case of epilepsy in an uncle. The neurological exam was entirely normal at that time.

Laboratory exams ruled out X-linked adrenoleukodystrophy and metachromatic leukodystrophy. Chromatography of amino acids in the blood and urine, among other results, did not clarify the diagnosis. The MRI with spectroscopy was repeated in 2006 and showed alterations suggesting VWM (Fig 1). A new MRI in July 2007 was unchanged (Fig 2).

Genetic analysis showed that the patient was compound heterozygous for two mutations in *EIF2B5*: 1) p.Arg113His, also present in father, and 2) p.Met608Ile, also present in the mother. These findings confirmed the diagnosis of VWM, as suggested by the MRI findings.

One year and half after the diagnosis the patient is still without symptoms and the neurological exam continues to be normal.

## ATAXIA DA INFÂNCIA COM HIPOMIELINIZAÇÃO CENTRAL ATÍPICA

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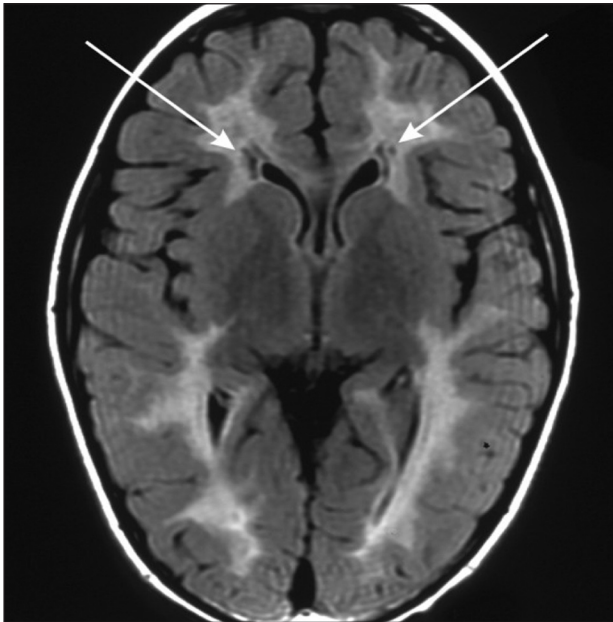


Fig 1. MRI 2006. White matter with signal intensity similar to the cerebrospinal fluid (arrow).

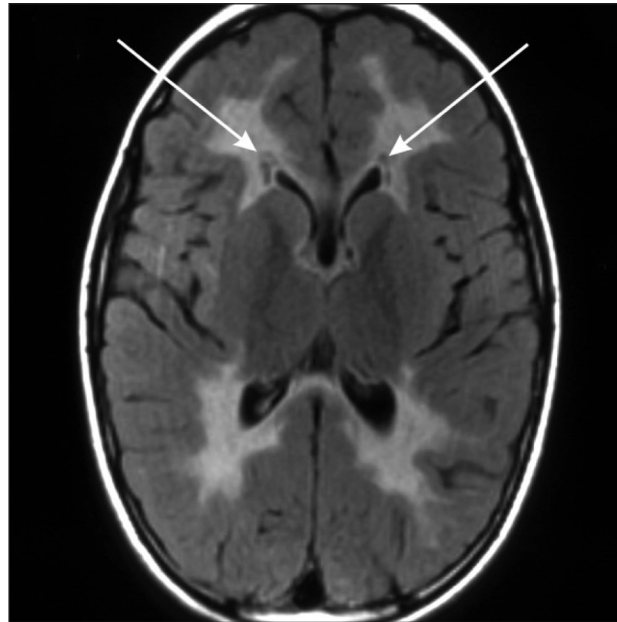


Fig 2. MRI 2007. Similar appearance to the preceding MRI.

## DISCUSSION

Pre-symptomatic cases have already been observed by many authors. van der Knaap et al. describe two of these cases in 1997 and one case in 1998<sup>11</sup>. In the article of 1998, 5 patients were analyzed who had a later onset of the disease; one of them had a normal life at the age of 22, but he was always clumsy in his motor activities and he also had learning difficulties. His neurological exam revealed, at the age of 22, minor cerebellar ataxia and brisk tendon reflexes of the legs. The MRI, made at the age of 21, presented typical image of VWM but with a milder degree of white matter involvement than observed in more serious cases. Except for one of the 5 patients, who died at the age of 16, the others were alive after the age of 20 years. All the patients, in that time, had motor signs. Wu and colleagues<sup>14</sup> described 1 case – among 9 patients – without clinical signs and with typical alterations on MRI. However, in all 9 patients the onset of the disease occurred between 6 months and 3 years of age and the deterioration was observed in all cases, after respiratory infection in 6 cases and light brain trauma in 3. A Brazilian paper, from Rosemberg et al.<sup>15</sup>, has also mentioned the alterations of the white matter that preceded the clinical symptoms in 2 of the 4 cases. In both cases the onset was between 8 and 34 months of age and characterized by cerebellar ataxia and spasticity.

The case of our patient does not fit entirely in the ones reported before. He was almost 9 years old when his complaint of feeling dizzy occurred. It lasted a few days and disappeared without treatment. Such symptom is not usually associated with the onset of VWM. The complaint

was not preceded by fever, trauma or any other kind of stress. The neurological exam did not demonstrate abnormality in any period and no motor deterioration was seen after 18 months. The MRI has also remained unchanged. The diagnosis would certainly not have been made if the patient would not have had an MRI, which in most cases is not requested for isolated dizziness.

Fogli and Boespflug-Tanguy<sup>5</sup> described 148 cases of VWM and demonstrated how important it is to pay attention to the diversity of clinical manifestations found in each case. A wide clinical spectrum has been observed in these patients, from congenital forms with rapid death to adult-onset forms with slow mental decline and progressive motor dysfunction, sometimes associated with congenital eye abnormalities or ovariodysgenesis. van der Knaap, Pronk and Scheper<sup>10</sup> agree with the wide phenotypic variability of VWM and they report that there is some genotype-phenotype correlation in VWM patients. Some mutations are consistently, although not invariably, associated with a mild phenotype whereas others mutations are consistently associated with a severe phenotype. But, the authors report that there is much variation between patients carrying the same mutations and between affected siblings in the same family. Consequently, environmental and other genetic factors influence the phenotype as well. The impression obtained from the literature studied and from the experience with our patient, whose diagnosis was unexpected, is that with MRI becoming more widely available more cases will be found with other unusual presentation.

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