



Case Report

Adult-onset vanishing white matter disease presenting as dementia

Soreya Belarbi*, Selma Dounia Bensemmane, Imene Bouguerra, Meriem Ouali and Samira Makri Mokrane

Department of Neurology, Ali Ait Idir Hospital, Algiers, Algeria

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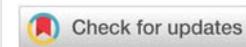
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*Corresponding author: Soreya Belarbi, Department of Neurology, Ali Ait Idir Hospital, Algiers, Algeria, E-mail: belarbi_soreya@yahoo.fr

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Abstract

Vanishing White Matter Disease (VWMD), also known as Childhood Ataxia with Central Hypomyelination (CACH) is a leukoencephalopathy with an autosomal recessive inheritance. It is caused by mutations in any of the five genes encoding the five subunits of the eukaryotic translational initiation factor 2B (eIF2B). Although VWMD was initially described in young children, it is now well known that it has a wide phenotypic spectrum, affecting people of all ages.

VWMD is typically characterized by normal or mildly delayed initial psychomotor development, followed by episodic or chronic neurological deterioration, often provoked by infections or minor head trauma. Neurological signs consist mainly of cerebellar ataxia and spasticity. There is no specific treatment beside the "prevention" of cellular stress. Therefore, early recognition of the diagnosis is important to avoid triggering factors and allow genetic counseling.

The reported case describes the clinical and radiological characteristics of a patient with adulthood onset of VWMD, revealed by subcortical dementia.

Introduction

Vanishing White Matter Disease (VWMD), also known as Childhood Ataxia with Central nervous system Hypomyelination (CACH), is an autosomal recessive leukoencephalopathy caused by mutations in one of five genes: *EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5*, located respectively on chromosomes 12q24.3, 14q24, 1p34.1, 2p23.3 and 3q27 [1-3]. Eukaryotic translation initiation factor 2B (EIF2B) is a key for the initiation of translation and the regulation of protein synthesis in response to cellular stresses [4]. Until now, more than 150 mutations in the 5 EIF2B genes have been reported [5,6]. The most common mutation in both children and adults is the p.Arg113His mutation of the EIF2B5 gene, generally associated with a relatively benign phenotype and slower course of the disease [7,8].

Although VWMD was initially recognized as a disease of young children, it has now become clear that there is an extreme variation in the phenotype and severity of the disease depending on the age of onset [9].

Four evolutionary groups have been defined: An early infantile form (age of onset < 1 year) [10], a late infantile form (age of onset: 2 to 4 years) corresponds to the classic form of CACH syndrome [11], a form of juvenile onset (age of onset: 5-15 years) [12] and a form onset in adulthood (age of onset : > 15 years) [13].

Severe forms of VWMD begin in the prenatal or infantile period and manifest as cerebellar ataxia and spasticity and then lead to early death [14]. The milder variants start in adolescence or adulthood and are characterized by slow disease progression [15].

The progression of leukoencephalopathy with vanishing white matter is generally variable with periods of relative stability interrupted by episodes of rapid decline. Stress, infection and head injury are known as stressors which could trigger a clinical / radiological decline.

These stresses can trigger the first symptoms of the disease or make existing symptoms worse.

The diagnosis of VWMD is primarily made by MRI due to



pathognomonic imaging, which is very specific to the disease. Brain MRI shows diffuse, bilateral and symmetric abnormalities of the cerebral white matter with signal similar to that of the Cerebrospinal Fluid (CSF): Hyposignal on T1, hypersignal on T2, *without any contrast enhancement after injection of the contrast medium*. Substantial impairment is predominant with respect for the U fibers and in subtentorial of the corticospinal bundles, cerebellum and spinal cord. On the FLAIR (fluid attenuated inversion recovery) sequences (or proton density), within white matter hypersignal abnormalities, there are extensive hypointense zones attesting to the cavity character of this leukodystrophy [16] in which the white matter is replaced by fluid [17]. Cavitory areas are preferentially found in the periventricular white matter mainly in frontal or sometimes occipital regions. The extensive character of white matter cavitation in infantile forms explains the term Vanishing White Matter, given to this syndrome. In juvenile / adult forms, cavitations can be absent or appear later [18–20].

In this paper, we are reporting a case of late-onset VWMD presenting slowly progressive cognitive defect with a neuropsychological profile of subcortical dementia.

Case report

A 41-year-old man was admitted to our neurology department due to the presence of memory impairment. He was the third child of consanguineous parents, originally from Bordj Menail, a city located in east of Algiers. In terms of development, the patient had normal psychomotor and language acquisitions. He worked as a farmer and then as a worker in a chocolate factory until 1 year ago, which corresponds to the beginning of the memory problems. There were no neurological or psychiatric disorder in the family.

The onset of the disorders dates back to the age of 40, marked by the progressive appearance of memory disorders relating to recent events “anterograde amnesia”, with inability to perform his work, as well as concentrating and decision making difficulties.

His family noticed a lack of personal hygiene as well as memory problems. He forgets what to buy and repeats the same things to himself. Subsequently, behavioral disorders appeared with a tendency to withdraw into oneself, a flat progressive affect and an amotivational state with lack of initiative. These disorders affected the basic activities of daily living. He had to stop all professional activity.

The evolution of the disorders was gradually worsening, with the appearance 6 months later of muscular weakness and stiffness of the lower limbs, markedly of the left with difficulty in walking.

He has no history of head trauma or episodic worsening after febrile illness.

Neurologic examination revealed brisk and exaggerated tendon reflexes, bilateral Babinski sign, and mild spastic gait.

We performed a neuropsychological workup, neuroimaging of brain and spine, a lumbar puncture with cytochemical and

immunological study of the CSF, an autoimmunity workup, an Eye exam (Slit lamp exam and fundus examination (to look for optic neuropathy and an Electroencephalogram (EEG).

We also performed thyroid hormones and Thyroid Peroxidase antibodies (TPO) assay, vitamin B12, folic acid and homocysteine assay, as well as leukocyte enzyme assay.

The neuropsychological assessment performed included a Mini-Mental State Examination (MMSE) for global assessment of cognitive functions, Nine Images Test (TNI-93) for assessment of episodic memory, *Digit Span Forward* and *Digit Span Backward* for assessment of short-term memory and working memory.

The Symbol Digit Modalities Test (SDMT) was used to assess divided attention, visual scanning, tracking and motor speed. The assessment of executive functions was made by the Frontal Assessment Battery (FAB), attention and mental flexibility by the Trail Making Test (TMT: TMT A / TMT B).

As for the language, it was evaluated by Verbal fluency (Categorical and Lexical).

The Bells Test, a cancellation task, allowed a quantitative and qualitative evaluation of visual neglect.

Result of neuropsychological assessment

The global cognitive assessment by MMSE revealed a score of 26/30 for a socio-cultural level NSC5 “11 years of studies”, with delayed recall failure that improved with clues. Language and praxis were preserved.

In addition, the neuropsychological assessment was in favor of subcortical dementia (Table 1), with a dysexecutive syndrome, including programming and planning disorders and loss of inhibitory control, a lack of access to the lexical

Table1: Neuropsychological assessment.

Tests	Scores
MMSE	25/30
FAB (frontal assessment battery)	11/18
• Motor series “Luria” test (programming)	1/3
• Go-No- Go (inhibitory control)	0/3
Trail Making Test (TMT)	Failure (131sc) Impossible
• TMT A	
• TMT B	
SDMT (Symbol digit modalities test)	7 correct answers in 90sc
Verbal fluency	Decreased
• Categorical (Animals in 2mn)	07
• Lexical (Letter P in 2mn)	01
Nine Images Test : TNI-93	
• Delayed recall	9/9
• Free recall 6	6
• Cued recall/ RI3	3
• Space recall	9/9
• Intrusions	0
Digit-span task	
• Forwards	4
• Backwards	2
The Bells test	30 answers (normal)

field with reduced verbal fluency, cognitive slowing down with slowness in the speed of information processing, as well as attention disorders.

Memory tests revealed immediate memory deficit with impaired working memory. The delayed memory (“episodic memory”) was preserved. Cortical functions, such as melokinetic, ideational, ideomotor and buccofacial praxies, visual gnosias, and expressive language, were relatively spared.

MRI study

The brain MRI finds a diffuse involvement of the cerebral hemispherical white matter, bilateral and symmetrical, predominantly periventricular, reaching the U-shaped fibers in places, presenting in T2 hypersignal and Flair, associated with atrophy with multiple cavitations of the white matter (Figure 1), dysgenesis of the corpus callosum which is atrophied, reduced to a thin millimeter band and absence of pathological enhancement. The spinal cord MRI hasn't shown abnormalities.

His blood investigations, including full blood count, renal panel, liver function test, folate, cobalamin and thyroid hormones were normal.

The cytochemical study of CSF (Protein: 0.54g/l, Cells: 0 elements /mm³) and immunological study are without abnormalities. Autoimmunity assessment is also without abnormalities.

Assessment of lysosomal enzymes, arylsulfatases A and B-galactosidases excluded metachromatic leukodystrophy and GM1 gangliosidosis.

Standby EEG

The trace is slowed down as a whole, without epileptic abnormalities.

Eye Exam was without anomalies.

Comment

VWMD is a rare disease that typically occurs in children presenting progressive and chronic cerebellar ataxia, spasticity, epilepsy, and relatively mild intellectual decline [17]. Adulthood onset VWMD is even rarer. It is estimated that it represents 15% of cases [21,22] and that it is characterized by a large phenotypic variability compared to early VWMD.

The clinical and neuroradiological characteristics of adult forms are insufficiently known. The initial manifestations could be complicated migraines, seizures [19], psychiatric disorders [23], dementia [24], motor deterioration, spasticity or cerebellar syndrome.

Women can rarely suffer from ovarioleukodystrophy syndrome [25], defined by the combination of slowly progressive leukodystrophy and ovarian failure. Ovarian failure is often indicative of the disease, in the form of primary or secondary amenorrhea with increased serum FSH / LH, and decreased

estradiol and progesterone. Morphological examinations may show ovarian atrophy. Neurological involvement is often secondary in the form of persistent headaches or cognitive or behavioral disorders. A correlation exists between the severity of ovarian failure and neurological disorders, especially early cognitive disorders.

Pauci-symptomatic forms, or asymptomatic, or even revealed by non-neurological symptoms, have also been described.

With the great phenotypic variability of late-onset VWMD, it can be difficult to make a clinical diagnosis.

It is now well established that the severity of the disease is inversely proportional to the age of onset [2]. Indeed, a late onset age is generally associated with a milder course of the disease [26]. Episodes of rapid deterioration are less frequent.

The last case of late-onset VWMD was reported in a 43-year-old patient with depressed mood, irritability, personality change with uncontrollable anger and disinhibition with coprolalia and cognitive decline. These were memory disorders relating to short-term memory and working memory, attention disorders and a reduced capacity for organization. These disorders were associated with progressive dystonia [27] and ataxia with postural instability and frequent falls.

In our patient, the disease began late at the age of 41 with mental decline and a slight pyramidal syndrome. The neuropsychological evaluation was in favor of a subcortical dementia marked by a dysexecutive syndrome. To our knowledge, this is the first case described in Algeria of VWMD beginning in adulthood with a dementia syndrome.

An observation of presenile subcortical dementia beginning at age 55, without other clinical abnormalities apart from a frustrated pyramidal syndrome has also been reported by Gascon-Bayarri J, et al. [28]. As reported in our patient, VWMD onset in adulthood presents earlier and more severe cognitive impairment than early onset disease [29].

The main diagnostic feature in our patient with subcortical dementia is an extensive leukoencephalopathy on cerebral MRI presenting low signal intensity on T1, high signal on T2, without contrast enhancement. Furthermore, it was noted the presence of a cavitory appearance on the Flair sequences, with the presence within the abnormal hypersignal of white matter, large areas of hyposignal. White matter had the same signal strength as CSF in all sequences. This signal behavior is characteristic of VWMD [9,18].

The diagnosis of VWMD is mainly made by MRI because of pathognomonic radiologic lesions, which are very sensitive and disease specific (Figures 1,2) [23]. This was very useful to us since it was impossible to perform a genetic study in the patient.

For neurologists, the aetiologic diagnosis of early onset dementia is a challenge that is sometimes not met until a post-mortem examination.

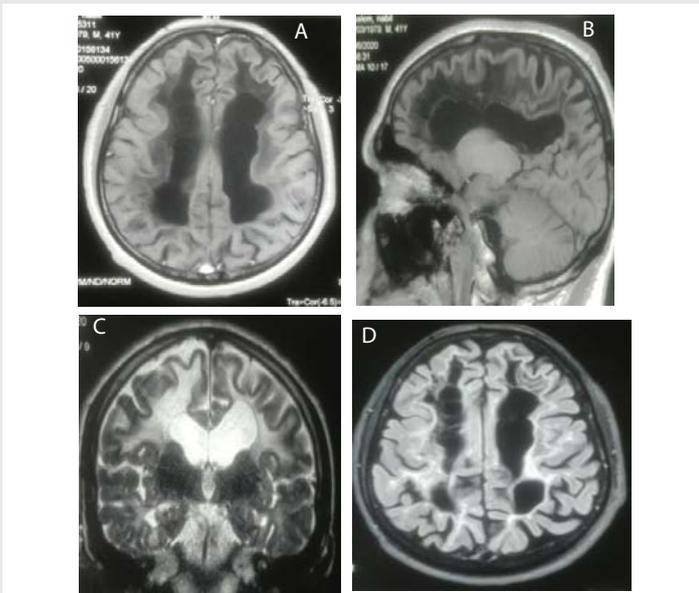


Figure 1: Brain MRI with diffuse and severe leukoencephalopathy as well as cavitating white matter degeneration with a signal similar to cerebrospinal fluid. (A-B) T1, (C) T2 and (D) fluid-attenuated inversion recovery sequences.

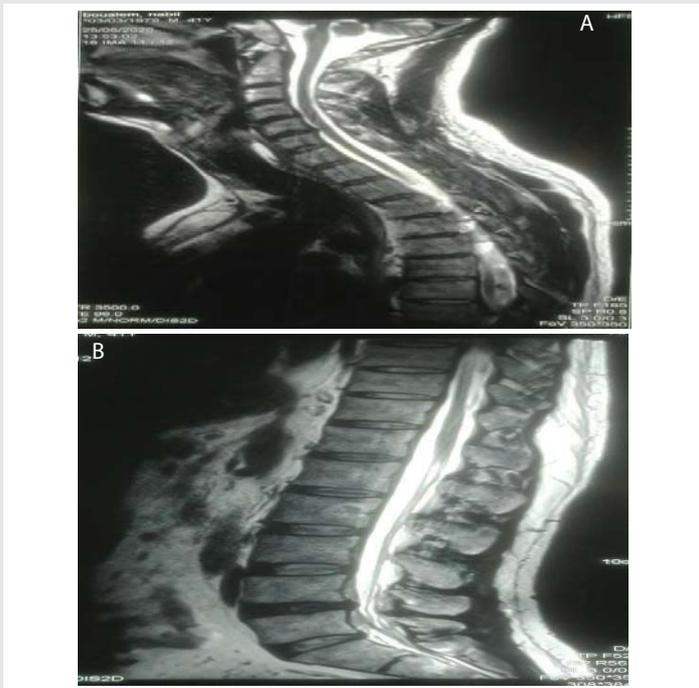


Figure 2: Normal Spine MRI.

There is currently no specific treatment for the disease to offer to patients. However, infections and other stressors should be strictly avoided.

Recent studies report that mitochondrial dysfunction and endoplasmic reticulum stress are strongly implicated in the pathology. Future treatment strategies involving compounds regulating EIF2 phosphorylation might benefit VWMD patients. A panel of candidate drugs, including berberine, deflazacort, ursodiol, zileuton, guanabenz and Anavex 2-73, and preclinical ISRIB (integrated stress response inhibitor), increased cell survival of *EIF2B5*^{R113H/A403V} or *EIF2B2*^{G200V/E213G} VWMD astrocytes,

and were further investigated for their effect on the integrated stress response and mitochondrial stress [30].

Conclusion

VWM disease shows a quite wide range of phenotypic variations. It affects all age groups.

The reported case broadens the phenotypic spectrum of late-onset VWMD, which can manifest a presenile dementia. The clinical and neuroimaging findings of patients with VWMD are highly specific, directing the diagnosis and avoiding unnecessary costs.

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