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

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Introduction

Vanishing White Matter Disease (VWMD), also known as Childhood Ataxia with Central Hypomyelination (CACH), is an autosomal recessive leukoencephalopathy 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 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 besides 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.
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]. Cavitary 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

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

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a large phenotypic variability compared to early VWMD.
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 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 hypesignal 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 cytchemical 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
GMI 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
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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 hypsignal 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.
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 EIF2B5R113H/A403V or EIF2B2G200V/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.

References


