GM2 gangliosidosis variant B1

Neuroradiological findings

Abstract  Variant B1 is a rare type of GM2 gangliosidosis. Clinically, it shows a wide spectrum of forms ranging from infantile to juvenile. We report the first magnetic resonance imaging (MRI) findings from three patients affected by GM2 gangliosidosis variant B1, two presenting with the infantile form and one with the juvenile form. The MRI appearances of the two patients with the infantile form disease are congruent with those reported for the early-onset type of both Tay-Sachs and Sandhoff diseases, and are characterized by early involvement of the basal ganglia and thalamus with cortical atrophy appearing later. In contrast, the patient with the juvenile form of variant B1 showed progressive cortical and white-matter atrophy of the supratentorial structures and, to a lesser extent, the infratentorial structures. No basal ganglia or thalamic anomalies were observed. Because in the adult forms of both Tay-Sachs and Sandhoff diseases a progressive cerebellar atrophy represents the only abnormality detectable, it appears that an MRI pattern peculiar to GM2 gangliosidosis can be defined. This pattern ranges from the basal ganglia injury associated with the early and severe demyelination process noted in the infantile form of the disease, to cerebellar atrophy with no supratentorial anomalies in the adult form. An “intermediate” MRI picture, with cortical atrophy and mild cerebellar atrophy, but without basal ganglia impairment, can be observed in the juvenile form. In addition, our investigations suggest that MRI abnormalities in GM2 gangliosidosis correlate with the clinical form of the disease rather than with the biochemical variant of the enzymatic defect.

Key words  GM2 gangliosidosis variant B1 · hexosaminidase · Tay-Sachs disease · Sandhoff disease · neurometabolic diseases · MRI

Introduction

GM2 gangliosidosis is a group of inherited disorders characterized by the intralysosomal accumulation of GM2 ganglioside due to a deficiency in β-hexosaminidase (HexA), which has an αβ dimeric structure. Three forms of GM2 gangliosidosis have been described on the basis of the type of enzymatic deficit: (i) β-hexosaminidase α-subunit deficiency (variant B, Tay-Sachs disease); (ii) β-hexosaminidase β-subunit deficiency (variant 0, Sandhoff disease); and (iii) GM2 activator deficiency (variant AB). A few patients present with normal production of an α-subunit that associates almost normally with the β-subunit but is devoid of catalytic activity. The resulting αβ dimer behaves like normal HexA in several respects (isoelectric point, activity with several artificial substrates), but is inactive with the physiological substrate ganglioside GM2 or with sulfated synthetic substrates (e.g., 4-methylumbelliferyl-N-acetyl-β-D-glucosamine–6-sulfate [4-MUGS]) [13]. This variant was first thought to be related to GM2 activator deficiency, but was later shown to be allelic with hexosaminidase α-subunit deficiency, and is therefore
referred to as variant B1. HexA is mainly involved in the
catabolic process of gangliosides (GAGs). Recently,
HexA has been found to be also involved in the physio-
logical role of dermatan sulphate degradation [11].Clin-
ically, infantile-onset GM2 gangliosidosis is character-
ized by early neuromotor deterioration with death
occurring at 3–4 years of age. The juvenile form, with
onset between 2 and 6 years, is characterized by gait in-
stability and speech disturbances followed by progres-
sive ataxia. In the chronic or adult form, onset is charac-
terized by dysarthria followed by slowly developing
ataxia. Psychiatric disturbances and dystonia may also
be observed [13]. GM2 gangliosidosis variant B1 shows
a wide spectrum of clinical syndromes, and most pa-
tients present with either the juvenile or infantile form
[13].

We here report the neuroradiological findings from
two new patients diagnosed with GM2 gangliosidosis
variant B1, presenting with either the infantile (two) or
juvenile (one) forms.

Case reports

■ Patient 1

The patient was the first child of healthy non-consan-
guineous parents. Both the pregnancy and delivery were
normal. Her birth weight was 3100 g, and head circum-
ference 33 cm. After essentially normal neuromotor de-
velopment, she presented in the fifth month of life with
progressive loss of acquired milestones and hypotonia.
Sleep disturbances with frequent waking during the
night occurred in the same period. Tonic seizures oc-
curred in the eighth month, and myoclonic jerks and
blinking at 12 months. EEG showed generalized parox-
ysmal activity. Several anti-epileptic drugs, such as val-
proic acid, vigabatrin, phenobarbital, and benzodi-
azepines, did not control seizures. From the age of 12
months, hypotonia was progressively replaced by spastic
tetraparesis. At 16 months, the child was helpless,
blind, and unresponsive. Cherry-red spots were present
in both macular areas. EEG recorded diffuse high-voltage
waves, more obvious in the left temporal region, in
which paroxysmal activity was also observed. The first
MRI was performed at the age of 11 months. Periven-
tricular and symmetric lobar hypomyelination was ap-
parent. In T2-weighted images, hyperintensity in the
posteromedial thalami and hypointensity in the ventral
thalamic nucleus were documented (Fig. 2A). The cor-
pus callosum was thinner than normal. A large arach-
noid cyst was visible at the tip of the left temporal lobe.
When the patient was two years old, EEG examination
Fig. 1 Patient 1 (16 months). A. T2-weighted sequence shows diffuse and sym-
metrical hyperintensity involving the post medial thalami, and corpus striatum. Short T2 relaxation times were seen in the ventral thalamic nucleus, resulting in hy-
pointensity. Furthermore, internal, medial, and lateral medullary laminae were hyperintense. Finally, the cor-
pus callosum was thinner than normal and a pineal cyst was apparent. No signs of atrophy were detected (Fig. 1 A, B). Biochemical measurements established HexA de-
ficiency in the leukocytes and skin fibroblasts using flu-
orogenic substrates 4-methylumbelliferyl-N-acetyl-α-
D-glucosamine (4-MUG) and 4-MUGS, and gel electrophoresis. HexA activity tested with 4-MUG was
794.2 nmol/mg per hour in leukocytes (normal range [n.r.] 644–1446) and 3487.4 nmol/mg per hour in fi-
broblasts (n.r. 3033.7–11039.3). In contrast, HexA activ-
ity tested with 4-MUGS was 5.8 nmol/mg per hour in
leukocytes (n.r. 128–327) and 20.3 nmol/mg per hour in
fibroblasts (n.r. 378–956). Molecular analysis confirmed
the diagnosis of GM2 gangliosidosis. The child died at
the age of three years of respiratory insufficiency.

■ Patient 2

This 26-month-old boy was born to healthy non-consan-
guineous parents after an uneventful pregnancy. His
birth weight was 3300 g, and head circumference 35 cm.
Neuromotor development was reported normal during
the first four months of life. A progressive neuromotor
deterioration occurred subsequently. At 15 months of
age, physical examination revealed severe psychomotor
delay with generalized hypotonia and low responsiv-
eness to his surroundings. Temporal lobe-related seizures
were observed. Cherry-red spots were present in both
macular areas. EEG recorded diffuse high-voltage
waves, more obvious in the left temporal region, in
which paroxysmal activity was also observed. The first
MRI was performed at the age of 11 months. Periven-
tricular and symmetric lobar hypomyelination was ap-
parent. In T2-weighted images, hyperintensity in the
post medial thalami and hypointensity in the ventral
thalamic nucleus were documented (Fig. 2A). The cor-
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