Abstract

Introduction: GM2 gangliosidosis B1 variant (GM2B1) is an autosomal recessive disorder due to deficiency of β-hexosaminidase A, leading to the lysosomal storage of GM2 gangliosides in neuronal tissue and neuronal death. Symptoms include progressive motor coordination impairment and neurodegeneration, in children with previously normal development, leading to early death.

Objective: Clinical characterization of patients with GM2B1 with a focus on epileptic manifestations.

Methods: A descriptive retrospective study was conducted, analyzing clinical records of patients diagnosed with GM2B1 and followed at our Hospital Neuropediatric Department in the decade 2013-2022.

Results: Four patients (three female) from three families diagnosed with GM2B1 were identified. The median age at diagnosis was 70 months. The most frequent symptoms at presentation were developmental regression (all children), language impairment (three), and epileptic seizures (two). Enzymatic deficiency in leukocytes and pathogenic variants in the HEXA gene were demonstrated in all cases. The pathogenic variant c.533G>A(p.R178H) in exon 5 was present in seven of the eight alleles. All patients experienced language impairment (Md=42 mos) with complete language loss (Md=78 mos). Loss of walking ability occurred in three patients (Md=96 mos). All patients experienced epileptic seizures during the course of the disease, with a median onset of seizures at 55 months. Initial seizures were classified as atypical absences (two), tonic seizures (one) and myoclonic seizures (one). Electroencephalographic evaluation revealed slow basal rhythm and focal paroxysmal activity in all cases. All were treated with antiseizure medication, two requiring a combination of three drugs.

Conclusion: GM2B1 encompasses a wide clinical spectrum, with heterogeneous age of symptom onset, clinical presentation and disease progression. Epilepsy is a common comorbidity in GM2B1, with variable seizure type and severity, and may be difficult to control. Timely diagnosis, coupled with multidisciplinary clinical follow-up, is crucial to improve quality of life of patients and enable genetic counseling.

Keywords: Gangliosidosis, Lysosomal Storage Disease, Sphingolipidoses, Neurodegeneration
Introduction

GM2-gangliosidosis B1 variant (GM2B1) is a rare autosomal recessive lysosomal storage disease due to β-hexosaminidase A deficiency.\(^1,2\) GM2B1 leads to GM2 gangliosides accumulation in neuronal tissue, resulting in neuronal death.\(^1\)

The B1 phenotype is enzymologically distinct in that β-hexosaminidase A activity is normal (or almost normal) if tested with conventional artificial substrates, but is inactive to hydrolyze natural GM2-ganglioside and sulfated artificial substrates (e.g., 4-MU-GlcNAc-6-sulfate).\(^3\)

B1 variant has a high incidence in Northern Portugal and is globally more frequent in southern Europe.\(^3,4\)

As with the other GM2 gangliosidosis, three forms of presentations can be distinguished of decreasing severity: infantile onset, with symptoms emerging between 4 and 8 months (mo) of age, characterized by early neurological deterioration and death in late infancy; juvenile onset, presenting between 2 and 10 years of age, with slower progression and death occurring between adolescence and early adulthood; and late onset, less common, manifesting in adolescence or adulthood, with a more indolent clinical course and variable survival.\(^2\)

Juvenile variants are associated with cerebellar dysfunction, spasticity and dementia. Symptoms include motor incoordination, progressive neurological and functional deterioration at varying rates in children with previously normal development, leading to early death.\(^2\) Children with GM2B1 may present with motor deficits, progressive muscle weakness, axial hypotonia, developmental regression, visual or hearing loss, hyperacusis with excessive startle, and dementia.\(^2\) Epilepsy is a frequent comorbidity.\(^5\)

Cherry red spots correspond to prominent storage in retinal ganglion cells and are not consistently present in all patients.\(^4,6\) Patients with infantile onset of the disease usually have the typical cherry-red spot, associated with faster neurological deterioration and death in childhood.\(^6,7\)

Patients with B1 variant account for most late infantile and juvenile cases of GM2 gangliosidoses.\(^1,6\)

The gold standard for diagnosis is the measurement of enzyme activity in leukocytes, fibroblasts, or chorionic villi.\(^2\) Sequencing of the HEXA gene confirms the diagnosis. Neuroimaging reveals basal ganglia atrophy, hypomyelination, and sometimes cerebral and cerebellar atrophy.\(^2\)

There is currently no approved specific treatment for GM2B1. Treatment is primarily supportive, including symptomatic management of epilepsy and behavioral disorders, physiotherapy, and nutrition.\(^2,6\)

Objective

Clinical characterization of patients with GM2B1 with a focus on epileptic manifestations.

Methods

A descriptive retrospective analysis of the electronic clinical records of the patients diagnosed with GM2B1 and followed at our Hospital Neuropediatric Department was conducted.

All patients diagnosed with GM2B1 between January 2013 and December 2022 were included.

Informed consent has been obtained from the parents or legal guardians for the publication of anonymised clinical data.

Neurodevelopmental assessment was made using Griffiths Mental Development Scales.

Statistical analysis of the data was conducted using Excel® software.
Results

Four patients (three females), from three families, diagnosed with GM2B1 were identified during the study period. Patients 1 and 2 are monozygotic twins. Consanguinity was not present in any family.

The most frequent symptoms at presentation were developmental regression (four), language impairment (three), frequent falls (two), seizures (two), and apraxia (two) (Table 1). First symptoms were noticed at a mean age of 42mo (36 to 48; median 42mo).

The median age at diagnosis was 70 mo (66 to 95).

Diagnosis was based on leukocyte b-hexosaminidase A enzyme activity measurement (all had enzymatic deficiency with the sulfatated substract) and HEXA gene sequencing.

The pathogenic variant c.533G>A(p.R178H) in exon 5 was present in seven of the eight alleles. (Table 1).

Table 1. Clinical, electroencephalographic, enzymatic and genetic characteristics of patients.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first symptoms</td>
<td>42 months</td>
<td>42 months</td>
<td>48 months</td>
<td>36 months</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>70 months</td>
<td>66 months</td>
<td>70 months</td>
<td>95 months</td>
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<tr>
<td>Present age</td>
<td>9 years</td>
<td>9 years</td>
<td>11 years</td>
<td>12 years</td>
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<tr>
<td>Initial symptoms</td>
<td>Developmental</td>
<td>Developmental</td>
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<tr>
<td></td>
<td>regression, language impairment, apraxia, frequent falls.</td>
<td>regression, language impairment, apraxia, frequent falls, seizures.</td>
<td>regression, language impairment, seizures.</td>
<td>regression, apraxia.</td>
</tr>
<tr>
<td>Age at first seizure</td>
<td>42 months</td>
<td>64 months</td>
<td>46 months</td>
<td>68 months</td>
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<tr>
<td>Type of seizures</td>
<td>Atypical absences</td>
<td>Tonic seizures</td>
<td>Myoclonic seizures</td>
<td>Atypical absences</td>
</tr>
<tr>
<td>Age at refractory epilepsy diagnosis</td>
<td>-</td>
<td>-</td>
<td>92 months</td>
<td>124 months</td>
</tr>
<tr>
<td>b-hexosaminidase A enzyme activity in leukocytes</td>
<td>(Reference range: 100-390)</td>
<td>(Reference range: 100-390)</td>
<td>(Reference range: 100-390)</td>
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<tr>
<td></td>
<td>4 nmol/h/mg protein</td>
<td>2 nmol/h/mg protein</td>
<td>4 nmol/h/mg protein</td>
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<td>Genetic test</td>
<td>c.533G&gt;A</td>
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<td>c.533G&gt;A</td>
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<tr>
<td>Brain imaging</td>
<td>Not done</td>
<td>18 months after onset</td>
<td>12 mo before clinical onset</td>
<td>84 mo after disease onset</td>
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<td></td>
<td></td>
<td>Normal Brain-CT</td>
<td>Normal Brain-MRI</td>
<td>Brain-CT: diffuse cortico-subcortical cerebral and cerebellar atrophy.</td>
</tr>
</tbody>
</table>

CT – Computed Tomography; EEG – electroencephalogram; FIRDA – Frontal Intermittent Rhythmic Delta Activity; HEXA - hexosaminidase A; mo – months; MRI – Magnetic Resonance Imaging.
Median diagnosis delay was 26 mo (22 to 59). At the end of the study, the patients’s median age was 8 years old. The median follow-up time after diagnosis was 5 years.

The median onset of language delay was 42 mo (36 to 48), with a median of total language loss by 78 mo (78 to 96). The median onset of cognitive decline was 51 mo (36 to 60). Three patients underwent serial cognitive assessments (Graphs 1 to 3).

**Graph 1.** Neurodevelopmental assessment of Patient 1 using Ruth Griffiths mental development scale – follow-up.

**Graph 2.** Neurodevelopmental assessment of Patient 2 using Ruth Griffiths mental development scale – follow-up.

**Graph 3.** Neurodevelopmental assessment of Patient 4 using Ruth Griffiths mental development scale – follow-up.
None of the patients had motor development delay in the first 6 months of life. The median age of walking onset was 17 mo (12 to 17). Loss of walking ability occurred in three children, with a median at 96 mo (92 to 103).

All patients presented muscle weakness, motor incoordination and gait disturbances during disease course. All experienced dysphagia, with a median onset at 82 mo (36 to 120).

All patients had seizures, with a median onset at 55 mo (36 to 68). Seizures were classified as atypical absences (two children), tonic seizures (one), and myoclonic seizures (one).

The electroencephalographic evaluation (Figures 1-4) showed slow basal rhythm and paroxysmal activity in frontal regions in all patients and Frontal Intermittent Rhythmic Delta Activity (FIRDA) pattern in two. All patients were treated with antiseizure medication (ASM), two requiring a combination of three ASM for seizure control.

All patients had ophthalmologic evaluation, which did not reveal abnormalities, particularly cherry-red spot.

During follow-up, brain imaging exams were conducted in three patients: two magnetic resonance and one computed tomography. Of these patients, one showed diffuse cortico-subcortical cerebral and cerebellar atrophy (Figure 5). The other three patients did not present any changes on neuroimaging.

**Figure 1.** Electroencephalographic evaluation of patient 1: slow basal rhythm associating FIRDA bursts indicating diffuse cerebral dysfunction.

**Figure 2.** Electroencephalographic evaluation of patient 2: slow basal rhythm associating FIRDA bursts indicating diffuse cerebral dysfunction.
Figure 3. Electroencephalographic evaluation of patient 3: paroxysmal activity in bilateral frontal regions.

Figure 4. Electroencephalographic evaluation of patient 4: bilateral frontal paroxysmal activity.

Figure 5. Brain CT sagittal and coronal cuts - patient 4: diffuse cortico-subcortical cerebral and cerebellar atrophy.
Discussion

All patients in this cohort presented the (early) juvenile onset form, has typically occurs in GM2B1. All patients had at least two symptoms at presentation, with a variable age of onset of each symptom. None exhibited the typical cherry-red spot, which is usually associated with the infantile form and faster neurological deterioration.

The first manifestation was loss of acquired skills in all patients, which is the hallmark of cerebral gangliosidosis. Language impairment and epileptic seizures were also present at presentation in most patients.

All patients showed progressive loss of motor ability and total loss of language. The neurodegenerative character of the disease was documented by serial cognitive assessments in three patients.

In this cohort, epilepsy was consistently present, although with a diverse clinical spectrum. The most frequent presentation was absence seizures, contrasting with previous studies, which reported generalized and myoclonic seizures as the most frequent. Seizures were controlled with ASM in all patients, with a high percentage of patients with difficult seizure control and requiring combination of three drugs.

Within our case series, only one patient (of three) had abnormal findings (dysmyelination, cerebellar and cerebral atrophy) in brain imaging commonly found in patients with juvenile onset. Brain MRI was normal in two patients probably due to the disease progression pattern presented and the time elapsed since first symptom onset. Moreover, abnormal findings in brain imaging of juvenile onset patients correlate with the presence of ataxia, not present at the time of the neuroimaging in those two patients.

Currently, no specific treatment is available for GM2B1 or other gangliosidoses. In our cohort, two patients required a combination of three ASM for seizure control, although other publications suggest that seizures usually respond to standard treatment. Inovative treatments are on trial, such as substrate reduction therapy (e.g. miglustat) and chaperone therapy (e.g. Pyrimethamine), although with no clinical improvement has been shown so far. Trials combining miglustat/ketogenic diet, venglustat (substrate reduction therapy for late-onset forms), and N-acetyl-Leucine (for cerebellar ataxia) are also in different stages of investigation for the treatment of GM2B1.

Diagnosis was based on of beta-hexosaminidase A deficiency towards the sulfated substrate and genetic confirmation in all patients. In our cohort, the pathogenic variant c.533G>A(p.R178H) in exon 5 of HEXA gene was present in seven of the eight alleles. The other variant, c.1496G>A(p.R499H) in exon 13, present in compound heterozygosity in one patient, as also been described associated with GM2.

Diagnosis was defined on average only 33 mo (median 26) after symptom onset. However, in other series described in the literature, the mean interval between symptom onset and diagnosis is 7.5 years.

The disease progression was variable, as described in the literature. All patients were alive by the end of this study, with a mean age of 130 mo. This previous unpublished case series of our department included 3 children, all with infantile onset which tend to have accelerated progression of the disease, explaining the 100% mortality rate of this previous data.

Diagnostic delay was too long, yet shorter than in other series. Early diagnosis of this neurodegenerative disease is essential for patient management and monitoring of disease progression. Multidisciplinary clinical supervision allows for improvement of patient’s quality of life, appropriate treatment of comorbidities, and addressing the special needs that arise in these patients. Prompt and correct diagnosis also allows for adequate genetic counselling, including reproductive options for the families.

Several lysosomal storage diseases are currently in the pipeline for inclusion in neonatal screening programs. This is not the case with GM2B1, as there is still no treatment that significantly modifies the natural history of the disease.
Conclusion

GM2B1 is a neurodegenerative disease characterized by a heterogeneous clinical spectrum, regarding age of symptom onset, clinical presentation, and disease progression. At presentation, all patients exhibited at least two symptoms. Epilepsy is a common comorbidity in GM2B1, with variable seizure types and severity and, although most patients respond to ASM, control may require the use of multiple drugs.

Prompt diagnosis, with multidisciplinary clinical follow-up, is crucial for improving patients’ quality of life and enabling timely genetic counseling.

In our country, due to the relative high frequency of variant B1 form of GM2-gangliosidosis, this diagnosis must be considered in face of clinical neurodegeneration associated with speech or gait disturbances, dystonia, seizures and/or pyramidal features.

Conflict of Interest

The authors declare they have no potential conflicts of interest to disclose.

References


Citation: Anjos MM, Ferreira S, Diogo L, Almeida J, Pereira C. Epilepsy and Cognition in GM2-Gangliosidosis B1 Variant - Experience of a Tertiary Hospital. SVOA Paediatrics 2024, 3:4, 89-96. doi:10.58624/SVOAPD.2024.03.071

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