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Case Report

GM2 activator deficiency: An ultra-rare disorder with a new case and review of 22 published cases

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ABSTRACT

GM2 activator deficiency (AB variant of GM2 gangliosidosis) is an ultra-rare autosomal recessive lysosomal storage disorder caused by pathogenic GM2A mutations. The loss of a functional GM2 activator protein disrupts GM2 ganglioside degradation, leading to progressive neurodegeneration. Although it shares clinical features with Tay-Sachs disease, GM2 activator deficiency remains a genetically and biochemically distinct disorder, with limited genotype-phenotype correlation due to the small number of reported cases.

This report presents a 33-month-old male with an infantile-onset phenotype, characterized by nystagmus, axial hypotonia, hyperacusis, and bilateral cherry-red spots. Genetic analysis identified a homozygous likely pathogenic c.262_264del (p.Lys88del) mutation, reinforcing its potential association with early disease onset. His clinical course was marked by progressive neurodegeneration, recurrent pulmonary infections, and severe feeding difficulties requiring gastrostomy placement.

In addition, previously published cases were reviewed to provide insights into the phenotypic spectrum, age of onset, and key clinical characteristics of GM2 activator deficiency. Among the 22 reported cases, 77.3 % exhibited an infantile-onset phenotype, while 18.2 % and 4.5 % had juvenile and adult-onset forms, respectively. Notably, cherry-red spots and hyperacusis were present in 94.1 % and 82.4 % of infantile cases but were strikingly absent in later-onset phenotypes.

This case report, supplemented by a literature review, offers a comprehensive overview of GM2 activator deficiency and underscores the importance of early molecular diagnosis in suspected cases

1. Introduction

GM2 activator deficiency (AB variant of GM2 gangliosidosis) is an ultra-rare autosomal recessive disorder caused by pathogenic variants in the *GM2A* gene [1]. The *GM2A* gene encodes the GM2 activator protein (GM2AP), a small lysosomal glycoprotein that serves as a cofactor for β-hexosaminidase A (HexA). GM2AP facilitates the degradation of membrane-bound GM2 ganglioside by solubilizing it and presenting it to HexA within the lysosomal compartment. In contrast to Tay-Sachs and Sandhoff diseases, where the enzymatic activity of HexA or HexB is primarily deficient, GM2 activator deficiency leads to impaired GM2 hydrolysis despite normal enzyme levels, due to the absence of this essential cofactor. As a result, GM2 accumulates in neurons, triggering progressive neurodegeneration [2,3].

Although its principal role lies in glycosphingolipid catabolism, GM2AP has also been implicated in lipid transfer and membrane remodeling, though these ancillary functions are not yet fully elucidated [4,5]. Animal models of GM2A deficiency exhibit specific cerebellar involvement, underscoring its critical role in neuronal integrity [3].

Since its first description in 1975, only 22 cases have been reported, demonstrating a broad clinical spectrum ranging from acute infantile to late-onset phenotypes [1,6,7]. Due to its rarity, the precise incidence of GM2 activator deficiency remains unknown. While establishing genotype-phenotype correlations is challenging, the c.262_264del (p.Lys88del) variant has been identified exclusively in patients with infantile-onset disease, suggesting a potential link to early and severe clinical presentation [8,9].

Most reported GM2A deficiency cases have been described individually, without systematic comparison of phenotype subtypes or detailed epidemiological analysis. In this report, we present a genetically

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confirmed infantile-onset case carrying the p.Lys88del variant, reinforcing its association with early disease presentation. We provide detailed clinical and neuroimaging findings and include a comparative literature review that highlights age-specific diagnostic clues, such as the presence of cherry-red spots and hyperacusis, which have not been comprehensively addressed in previous publications. This case offers one of the most detailed phenotypic characterizations to date and contributes to a deeper understanding of the clinical and genetic spectrum of this ultra-rare disorder.

2. Case presentation

A 33-month-old male patient of Syrian descent presented with nystagmus and progressive neurodevelopmental delay. He was born at term via spontaneous vaginal delivery with a birth weight of 3000 g. In the neonatal period, he was admitted to the neonatal intensive care unit due to neonatal sepsis. His parents were first-degree cousins, and he had two healthy siblings. The patient exhibited significant global developmental delay. He achieved head control at 12 months but never acquired sitting or walking skills. At 13 months, his weight was −2.5 SDS, height was 0.1 SDS, and head circumference was −1.1 SDS. On neurological examination, he had axial hypotonia. Deep tendon reflexes were absent, and musculoskeletal evaluation showed a high-arched foot with hammer toe deformity. Hyperacusis was noted, and fundoscopic examination revealed bilateral cherry-red spots. Brain imaging at 14 months revealed prominent central and bilateral frontotemporal peripheral cerebrospinal fluid spaces on magnetic resonance imaging (MRI). Magnetic resonance spectroscopy was unremarkable. Electrophysiological studies showed the absence of P2 wave responses in both visual evoked potentials, indicating an abnormal visual pathway. Brainstem auditory evoked response testing revealed a V wave at 20 dBnHL in the right ear and 30 dBnHL in the left ear. Electromyography findings were normal. Metabolic investigations, including lysosomal enzyme analysis for Tay-Sachs and Sandhoff disease, were normal. Whole-exome sequencing (WES) identified a homozygous likely pathogenic c.262_264del (p.Lys88del) inframe deletion in the *GM2A* gene, and parental genetic analysis confirmed a heterozygous carrier status in both parents. The patient's clinical course was characterized by progressive neurodegeneration. Over time, he lost head control, and his hospital admissions increased due to recurrent pulmonary infections. By 30 months of age, he developed significant feeding difficulties requiring gastrostomy placement. His neurological deterioration continued, with worsening spasticity and loss of motor function.

3. Discussion

GM2 activator deficiency (AB variant of GM2 gangliosidosis) is an ultra-rare autosomal recessive lysosomal storage disorder first described in 1975 by de Baecque et al. [1] Due to its rarity, only a limited number of cases have been reported, making genotype-phenotype correlations difficult [6]. In this study, we contribute to the existing literature by presenting a new infantile-onset case with a homozygousp Lys88del mutation, further supporting its potential association with early disease onset.

A summary of previously published cases is provided in Table 1, outlining the genetic and clinical spectrum of GM2 activator deficiency. To date, 22 cases have been reported in the literature, primarily classified into acute infantile (77.3 %), juvenile-onset (18.2 %), and late/adult-onset (4.5 %) phenotypes [6,10,11]. The age of onset ranged from 1 month to 10 years. The mean onset age was approximately 8.6 months in acute infantile cases and 7.2 years in juvenile and adult-onset cases. Cherry-red spots and hyperacusis were almost exclusively observed in acute infantile cases (94.1 % and 82.4 %, respectively), but were absent in later-onset phenotypes. This suggests that these features may be hallmarks of early-onset GM2 activator deficiency, whereas later-onset phenotypes might follow a distinct neuropathological course [6,7,10].

Notably, a similar phenotype-dependent pattern has been reported in other forms of GM2 gangliosidosis, including *HEXA*- and *HEXB*-related disorders. In infantile forms, severe GM2 accumulation leads to early involvement of retinal ganglion cells and auditory pathways, explaining the high frequency of cherry-red spots and hyperacusis. In contrast, these features are rarely seen in juvenile and late-onset forms, possibly reflecting slower substrate accumulation due to partial enzyme activity or other modifying factors [12,13]. Although GM2A deficiency involves normal HexA enzyme levels, the absence of the GM2 activator protein likely results in a comparable burden of substrate accumulation in early-onset cases, whereas slower accumulation in later-onset cases might limit involvement of specific tissues such as the retina and auditory system.

Among the reported cases, a significant proportion were of Middle Eastern, South Asian, and Mediterranean descent, with multiple cases described in Saudi Arabian, Indian, Turkish, and French Canadian populations [5–7,14]. Additionally, more than half of the reported cases were born to consanguineous parents, consistent with the recessive inheritance pattern of the disease.

The c.262_264del (p.Lys88del) variant is among the most frequently reported GM2A mutations, and notably, it has been identified exclusively in infantile-onset cases [8,9]. Although establishing a definitive genotype-phenotype correlation remains challenging due to the limited number of cases, the fact that our patient also exhibited an infantile phenotype supports the possibility that p.Lys88del may be associated with early-onset disease.

Clinically, our patient exhibited a typical acute infantile presentation, including neurodevelopmental regression, axial hypotonia, hyperacusis, and cherry-red spots. The disease course was characterized by progressive neurodegeneration, loss of motor function, feeding difficulties requiring gastrostomy, and recurrent pulmonary infections. These findings align with previously reported cases carrying the p.Lys88del mutation and further support its potential association with a severe, rapidly progressive disease course [8,9].

Previous functional studies provide further evidence for the pathogenicity of this in-frame deletion. Schepers et al. [8] demonstrated that the p.Lys88del variant leads to misfolding and endoplasmic reticulum-associated degradation of GM2AP, preventing its maturation and lysosomal localization. Biochemical assays revealed that this mutant protein retains only ~8 % of the normal cofactor activity. Crystallographic and biophysical studies have shown that GM2AP adopts a β-cup (or "cup-like") conformation with a central hydrophobic cavity, which is essential for solubilizing GM2 ganglioside and presenting it to HexA [15,16]. Lys88 is located within a structurally conserved region thought to stabilize this conformation. Its deletion likely disrupts the integrity of the lipid-binding pocket, contributing to the severe functional loss observed. These findings were later confirmed in a second patient with a similar phenotype [9], supporting the deleterious effect of the mutation despite its in-frame nature.

When cherry-red spots and hyperacusis are observed in infants with developmental regression, clinicians should consider lysosomal storage disorders in the differential diagnosis. These include GM1 gangliosidosis, GM2 gangliosidosis (Tay-Sachs disease, Sandhoff disease, GM2 activator deficiency), Niemann-Pick disease type A, and sialidosis and other conditions such as galactosialidosis, metachromatic leukodystrophy, multiple sulfatase deficiency, Farber disease, and Wolman disease [17]. One of the key diagnostic challenges of GM2 activator deficiency is its clinical resemblance to Tay-Sachs disease, as both conditions may present with progressive hypotonia, neuroregression, hyperacusis, and cherry-red spots. While Tay-Sachs is caused by mutations in the HEXA gene, resulting in reduced HexA activity, GM2A deficiency shows normal HexA levels [14]. This makes enzyme analysis insufficient for differentiation, and molecular testing becomes essential for an accurate diagnosis. WES confirmed the diagnosis in our patient after normal enzymatic assays, demonstrating the importance of early molecular

Table 1
Reported cases of GM2 activator deficiency.

Patient No	Year	Author(s)	Ethnicity	Age of Onset	Gender	Parental consanguinity	Clinical Presentation	Cherry red spots	Hyperacusis	Genetic Mutation(s)	Diagnostic Method	Patient Outcome
1.	1975	de Baecque et al. [1,20]	African-American	9 mo	F	No	Acute infantile	Yes	Yes	c.412 T > C	Enzyme/ histopath	Died by 14 mo
2.	1980	Goldman et al. [21] (Case 1)	Puerto Rican	2 y	M	No	Acute infantile	Yes	Not identified	Not identified	Enzyme/GM2 studies	Died at 4.5 y
3.	1980	Goldman et al. [21] (Case 2)	African-American	9 mo	F	No	Acute infantile	Yes	Yes	Not identified	Enzyme/GM2 studies	Died by 3.5 y
4.	1982	Hechtman et al. [22]	Canadian	14 mo	M	Not reported	Acute infantile	Yes	Not reported	Not identified	Biochem.	Died by 27 mo
5.	1993	Schröder et al. [23]	Indian	5 mo	F	No	Acute infantile	Yes	Yes	c.506G > C	GM2A sequencing	Died by 5.5 y
6.	1996	Schepers et al. [8] (Case 1)	Saudi	8 mo	F	Yes	Acute infantile	Yes	Yes	c.262_264del	Sequencing/ functional	Died ~2 y
7.	1996	Schepers et al. [8] (Case 2)	Spanish	7 mo	F	Yes	Acute infantile	Yes	Yes	c.410del	Sequencing/ functional	Died ~3 y
8.	1999	Sakuraba et al. [24]	Japanese	1 mo	Not stated	Not stated	Acute infantile	Yes	Yes	Not reported	Biochem.	Not stated
9.	1999	Chen et al. [25]	Laotian	5 mo	M	No	Acute infantile	Yes	Yes	c.160G > T	GM2A sequencing	Died ~2–3 y
10.	2008	Kolodny et al. [26]	Indian	15 mo	F	No	Acute infantile	Yes	Yes	c.521 T > G	Genetic	Not stated
11.	2015	Renaud & Brodsky [27]	Hmong	~4 mo	F	No	Acute infantile	Yes	Yes	c.160G > T	Gene seq.	Died by 2 y
12.	2015	Salih et al. [7] (Case 1)	Saudi	7 y	F	Yes	Juvenile-onset	No	No	c.164C > T	WES	Died by 18 y
13.	2015	Salih et al. [7] (Case 2)	Saudi	8 y	F	Yes	Juvenile-onset	No	No	c.164C > T	WES	Alive at 17 y
14.	2015	Salih et al. [7] (Case 3)	Saudi	8 y	M	Yes	Juvenile-onset	No	No	c.164C > T	NGS	Alive at 14 y
15.	2017	Brackmann et al. [9] (Case 1)	Turkish	9 mo	F	Yes	Acute infantile	Yes	Yes	c.262_264del	Gene seq.	Alive at 20 mo
16.	2017	Brackmann et al. [9] (Case 2)	Turkish	10 mo	F	Yes	Acute infantile	Yes	Yes	c.369_371delinsATTAA	Gene seq.	Alive at 14 mo
17.	2017	Kochumon et al. [14]	Indian	7 mo	F	Yes	Acute infantile	Yes	Yes	c.243-2A > T	Gene seq.	Alive at 20 mo
18.	2017	Martins et al. [5]	French Canadian	3 y	M	No	Juvenile-onset	No	No	c.259G > T / c.164C > T	WES	Alive at 9 y
19.	2021	İnci et al. [6] (Case 1)	Turkish	8 mo	M	Yes	Acute infantile	Yes	Yes	c.369_371delGCCinsTAA	Gene panel	Not stated
20.	2021	İnci et al. [6] (Case 2)	Turkish	9 mo	F	Yes	Acute infantile	Yes	Yes	c.369_371delGCCinsTAA	Gene testing	Not stated
21.	2022	Ganne et al. [10]	French	10 y	M	No	Late-onset	No	No	c.79 A > T / c.415C > T	WES	Alive at 24 y
22.	2023	Chen et al. [11]	Chinese	2 mo	F	No	Acute infantile	Yes	Yes	exon 2 del	WES	Alive at 7 mo
23.	Current case	Yoldas Celik et al.	Syrian	13 mo	M	Yes	Acute infantile	Yes	Yes	c.262_264del	WES	Alive at 33 mo

testing in suspected cases.

To date, no clinical or preclinical data support the efficacy of substrate reduction (e.g., Miglustat) or neuroprotective therapies (e.g., *N*-acetyl-DL-leucine) in GM2A deficiency. Although these agents have been explored in other forms of GM2 gangliosidosis, including Tay-Sachs and Sandhoff diseases [18], their potential utility in GM2A deficiency remains unknown. This is partly due to the rarity of the condition and the lack of experimental models specific to GM2AP deficiency, which limits the assessment of therapeutic interventions. However, recent preclinical studies have explored the potential of gene therapy using AAV9-GM2A vectors, demonstrating reduced GM2 accumulation and long-term transgene expression in an ABGM2 mouse model [19]. These findings highlight the possibility of future therapeutic interventions for this ultra-rare disorder, although further research is required to evaluate its clinical applicability.

In conclusion, our case represents a severe, early-onset form of GM2 activator deficiency associated with the p.Lys88del mutation, consistent with previous reports. The presence of p.Lys88del exclusively in infantile cases, including our patient, suggests a potential association with early disease onset. The absence of cherry-red spots and hyperacusis in juvenile and adult-onset cases highlights phenotypic distinctions in later-onset disease. Given the overlap with Tay-Sachs disease, genetic testing is essential for an accurate diagnosis, mainly when inconclusive enzyme assays. Further studies and case reports will be essential to better define the natural history, genotype-phenotype correlations, and potential therapeutic strategies for this rare disorder.

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Contribution Statement

M.Y.C. designed the study; M.Y.C., B.K., E.B and K.Y. collected and analyzed data; M.Y.C. wrote the manuscript. All authors read and approved the final manuscript.

Declaration of generative AI and AI-assisted technologies

The authors declare that they did not use artificial intelligence in the writing process.

CRediT authorship contribution statement

Merve Yoldaş Çelik: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Burcu Köşeci:** Formal analysis, Data curation, Conceptualization. **Ezgi Burgaç:** Formal analysis, Data curation, Conceptualization. **Kanay Yararbaş:** Data curation.

Informed consent

Informed consent was obtained from the patient's family and patient in the study.

Ethical approval

The local Institutional Review Board deemed the study exempt from review.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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