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Case Report

The 30th Case of Autosomal Dominant Gabriele-de Vries Syndrome: Diagnosis and Management in a 16-Month-Old Lebanese Boy

Lynn Srour, Khaled Baroudi, Ahmad Saleh, Rouba Shaker, Rena Mokbel, Chadi AL Alam*

Department of Pediatric Neurology Division, American Center for Psychiatry and Neurology, UAE and Haykel Hospital, Lebanon

***Corresponding Author:** Chadi AL Alam, Department of Pediatric Neurology Division, American Center for Psychiatry and Neurology, UAE and Haykel Hospital, Lebanon.

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Abstract

Gabriele-de Vries Syndrome (GADEVS) is a rare neurodevelopmental disorder caused by mutations in the YY1 gene, characterized by developmental delays, neurological issues, and various congenital anomalies. We report a case of a 16-month-old boy with GADEVS who exhibited poor sucking in infancy, delayed developmental milestones, central hypotonia, ataxic gait, and speech delay. MRI findings included mild dilation of the lateral ventricles and increased signal intensity in the white matter. Whole exome sequencing identified a heterozygous truncating mutation in the YY1 gene, confirming the diagnosis. This case highlights the importance of genetic testing for accurate diagnosis and underscores the need for a multidisciplinary approach to management, as well as further research to improve understanding and treatment of GADEVS.

Keywords: Gabriele-de Vries Syndrome (GADEVS); Lebanon

Case Presentation

The patient is a 1-year-4-month-old Lebanese baby boy, born full-term via normal vaginal delivery. Throughout the pregnancy and delivery, no complications were reported. However, the mother noted decreased fetal activity in the last trimester, although follow-up ultrasounds appeared normal. At birth, the baby's weight was 2.9 kg with normal height. He experienced poor sucking during the first three months of life, gradually improving over time. Psychomotor therapy was initiated at 13 months of age due to delayed developmental milestones. At 15 months, he achieved the milestone of sitting with support, followed by crawling at 16 months. The patient has not exhibited any speech development yet. The family history is negative for similar conditions, and there has been no exposure to screen time. His diet primarily consists of milk formula and soft foods.

Upon neurological examination, the patient has facial asymmetry, appears active with good eye contact and responsiveness to stimuli. However, central hypotonia and lack of coordination are evident, presenting an ataxic gait. He demonstrates adequate hand use but exhibits neglect of his lower extremities.

Metabolic panel results including serum amino acids, urine organic acids, ammonia, lactate, and pyruvate were within normal limits. MRI brain imaging revealed several notable findings.

Small mega cisterna magna, enlargement of the extra-axial pericerebral spaces, particularly in the frontal lobes, mild dilation of the lateral ventricles, Foci of increased signal intensity in the white matter adjacent to the occipital horns and trigones, small mega cisterna magna.

Enlargement of the extra-axial pericerebral spaces especially in the frontal lobes with widening of the prepontine cistern and cerebellopontine angles, and heterogeneous signal intensity of the CSF on the T2 analysis, as well in the aqueduct of Sylvius, without evidence of a space occupying process or clear obstruction. The corpus callosum is complete, however mildly thinned and showing upward bowing.

Additionally, whole exome sequencing identified a heterozygous variant of uncertain significance in the YY1 gene (NM_003403.4:c.1024C>T; p.(Arg342*)).

Based on the clinical presentation, MRI findings, and genetic testing results, the patient is diagnosed with autosomal dominant Gabriele-de Vries syndrome.

Discussion

Gabriele-de Vries Syndrome (GADEVS) is a neurodevelopmental disorder primarily caused by de novo mutations in the YY1 gene, located on chromosome 14q32. It is inherited in an autosomal dominant manner and typically features a spectrum of clinical manifestations including neurological problems, developmental delays, intellectual disabilities ranging from mild to severe, and various behavioral problems such as anxiety, autism-like behaviors, and attention-deficit/hyperactivity disorder. To date, de novo pathogenic variants in YY1 were identified in 0.03%-1% of individuals with unexplained intellectual disability in diverse studied cohorts [2].

Patients with GADEVS often exhibit a collection of dysmorphic facial features including facial asymmetry, broad forehead, down slanted palpebral fissures, and thick lips. About half of affected individuals had neurologic problems [1] characterized by motor delays, abnormal gait, hypotonia, and in some cases, more severe movement disorders like dystonia. Speech delays are common, and some individuals show severe cognitive impairment and are nonverbal. GADEVS also involves a variety of congenital abnormalities affecting multiple organ systems. These include, but are not limited to, skeletal anomalies (unilateral hemihypertrophy of lower limbs, increased laxity of fingers, hallux valgus, sandal gap), congenital heart defects (patent foramen ovale, Ebstein's anomaly), renal anomalies (hydronephrosis), endocrine (hypothyroidism), ocular abnormalities (strabismus, hypermetropia, astigmatism) and others (recurrent infections, breast hypoplasia, hyperextensible skin) [1].

Brain imaging often reveals non-specific abnormalities such as delayed myelination, enlarged ventricles, cortical dysplasia, focal areas of encephalomalacia, lateral ventricular dilatation, white matter atrophy, and agenesis of the corpus callosum [3].

Diagnostic criteria for GADEVS focus on the genetic detection of pathogenic variants of the YY1 gene through methods like exome sequencing or targeted gene panels. De novo heterozygous mutations, including missense and truncating mutations, disrupt the gene's function, often resulting in haploinsufficiency [1]. The mutation types in the YY1 gene of 29 patients were reviewed [3], including 16 missense mutations, nine frameshift mutations, two nonsense mutations, one 3-bp deletion and one mutation located in initiation codon. Notably, the mutant bases of 13 patients were located in exon 5, and those of 8 patients were in exon 4, which suggests that these exons might be mutation hotspots of YY1.

Management of GADEVS involves a comprehensive approach aimed at addressing individual symptoms and comorbidities associated with the condition. Interventions typically focus on symptomatic management such as intellectual disability, behavioral difficulties, craniofacial dysmorphisms, congenital anomalies, growth issues and feeding problems through targeted therapies and multidisciplinary interventions [4]. Genetic counseling is also crucial, offering information, coping strategies, and guidance on potential medical and developmental interventions to affected individuals and their families. The establishment of a database to collect detailed clinical information on additional individuals with YY1 mutations indicates ongoing efforts to better understand the clinical spectrum of GADEVS, potentially leading to improved management and treatment strategies in the future.

The presented case of a 1-year-4-month-old boy with Gabriele-de Vries Syndrome (GADEVS) exhibits remarkable consistency with the characteristics documented in the literature. Notably, the developmental delays, such as delayed sitting and crawling, align with previously reported psychomotor developmental issues in other GADEVS patients. Similarly, the patient's central hypotonia, ataxic gait, speech delay and poor sucking are characteristic neurological and developmental signs observed in the syndrome. Furthermore, the MRI findings of mild dilation of the lateral ventricles and increased white matter signal intensity mirror the non-specific brain imaging abnormalities frequently noted in other cases. The identification of a heterozygous truncating mutation in the YY1 gene provides a genetic confirmation of GADEVS, aligning with the reported pathogenic mechanism of haploinsufficiency documented in other patients. These parallels not only reinforce the accuracy of the diagnosis but also emphasize the importance of genetic testing in the assessment and management of suspected cases.

We reviewed the cases diagnosed with GADEVS throughout the literature and compiled a comprehensive table comparing the clinical features and pertinent information from these cases to our own clinical case. Notably, 29 patients have been previously diagnosed with GADEVS, and our patient represents the 30th case. Table 1 and Table 2 are attached.

The dataset analyzed in this study was derived from Yang et al. and supplemented with data from an additional 28 individuals re-

Study	Individual ID	Sex	Genotype	Exon
Gabriele., *et al*.	Individual–1	F	c.958C > T(p.His320Tyr)	4
	Individual–2	M	c.1015A > C(p.Lys339Gln)	4
	Individual–3	M	c.1097 T > C(p.Leu366Pro)	5
	Individual–4	F	c.1096C > G(p.Leu366Val)	5
	Individual–5	M	c.1138G > T(p.Asp380Tyr)	5
	Individual–17	F	c.385delG(p.Asp129Ilefs*127)	1
	Individual–18	M	c.1173delT(p.Asn391Lysfs*10)	5
	Individual–26	F	c.1030C > T(p.Gln344*)	4
	Individual–27	F	c.535A > T(p.Lys179*)	1
	Individual–28	M	c.1174-1176del(p.Lys393del)	5
Cherik., *et al*.	Individual–6	F	c.1007A > G(p.Glu336Gly)	4
	Individual–7	F	c.1112G > A(p.Arg371His)	5
	Individual–8	F	c.1001 T > C(p.Phe334Ser)	4
	Individual–9	M	c.1067C > T(p.Thr356Met)	5
	Individual–10	M	(p.Val374Gly)	5
	Individual–11	M	(p.His320Arg)	4
	Individual–12	M	c.1124G > A(p.Arg375Gln)	5
	Individual–13	M	c.908G > T(p.Cys303Phe)	4
	Individual–19	F	c.1151-1154dup(p.Pro386Valfs*7)	5
	Individual–20	M	c.690dup(p.Asp231Argfs*3)	2
Maria Teresa., *et al*.	Individual–14	F	c.907 T > C(p.Cys303Arg)	4
Li Tan., *et al*.	Individual–15	F	c.1124G > A(p.Arg375Gln)	5
Suely Rodrigues., *et al*.	Individual–16	F	c.1106A > G(p.Asn369Ser)	5
Morales-Rosado., *et al*.	Individual–21	F	c.860-864delTTAAAA(p.Ile287Argfs*3)	3
Surya., *et al*.	Individual–22	F	c.690delA(p.Glu231Ilefs*25)	2
Giovanna., *et al*.	Individual–23	M	c.1118-1119delAT(p.His373Argfs*18)	5
Hossein., *et al*.	Individual–24	M	c.690delA(p.Glu231Ilefs*25)	2
Nenad Koruga., *et al*.	Individual–25	M	c.1A > C(p.Met?)	1
Yang., *et al*.	Individual–29	F	c.458_476del (p. V153fs*97)	1
Proband		M	c.1024C>T (p. Arg342*)	4

Table 1: Overview of Individual Genetic Variants from Various Studies.

System	Symptoms	Yang., *et al*. Table 1[a]	Our study (+/–)
Growth	Birth weight in g (<2SD)	7/26	-
Nervous system	Motor delay	26/29	+
	Delayed speech and Language development	28/28	+
	Intellectual disability	23/27	N/A
	Behavioral abnormality	18/27	-
	Abnormal movement	11/26	+
	Abnormal brain MRI	11/22	+
Musculature	Hypotonia	13/28	+

Head and Neck	Broad forehead	25/29	+
	Facial asymmetry	13/29	+
	Broad nasal tip	18/29	+
	Thick lower lip vermilion	13/29	–
	Pointed chin	11/29	+
	Ear abnormality	23/28	–
Miscellaneous	Cardiac abnormality	5/23	-
	Feeding difficulties	22/26	+
	Recurrent infections	5/22	-
	Eye abnormalities	17/24	-
	Skeletal abnormalities	22/26	-

Table 2: Comparison of Clinical Symptoms in Patients Reported Previously in the Literature and in Our Study.

ported in 10 separate articles, resulting in a total sample size of 29 individuals. It should be noted that the frequency of occurrence for each symptom does not total 29 in some cases, due to certain symptoms being either not applicable or not available (N/A) for specific individuals.

Conclusion

The case of the 16-month-old boy diagnosed with autosomal dominant Gabriele-de Vries Syndrome (GADEVS) highlights the critical role of genetic testing in identifying this rare neurodevelopmental disorder. His symptoms—developmental delays, central hypotonia, ataxic gait, and speech delay—align with typical GADEVS presentations, as do his MRI findings of mild lateral ventricle dilation and increased white matter signal intensity.

The identification of a heterozygous variant in the YY1 gene confirmed the diagnosis, emphasizing the importance of exome sequencing. Managing GADEVS requires a multidisciplinary approach to address the diverse symptoms and associated conditions, with genetic counseling providing essential support to families.

This case underscores the need for ongoing research and data collection to better understand GADEVS and improve management strategies, ultimately enhancing the quality of life for affected individuals.

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