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Case Series

First Reported Lebanese Cases of Kleefstra Syndrome Type 2, with two Novel Variants of the KMT2C Gene

MOUAWAD Mayssi[1], SLAIBY Louis[1], AL KARI Georges[1], SNAIFER Patrick[1-2], MEGARBANE Andre[3-4], MANSOUR Hicham[1-5*]

[1]Faculty of Medicine, Saint George University of Beirut, Lebanon.

[2]Department of ENT, Head and neck surgery, Saint George University Medical Center, Lebanon.

[3]Department of Human Genetics, Gilbert and Rose-Marie Chagoury School of Medicine, Lebanese American University, Lebanon.

[4]Institut Jerome Lejeune, Paris, France.

[5]Department of Pediatrics, Saint George University Medical Center, Lebanon.

***Corresponding Author:** MANSOUR Hicham, Department of Pediatrics, Saint George University Medical Center, Lebanon.

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Abstract

Kleefstra syndrome type 2 (KLEFS2) is a rare neurodevelopmental disorder associated with pathogenic variants in the KMT2C gene. Its clinical spectrum remains incompletely defined due to the limited number of reported cases. Here we report two male patients presenting with global developmental delay and significant expressive language impairment. The first patient demonstrated early developmental regression, macrocephaly, persistent lactic acidosis, and a large hypopigmented cutaneous lesion. Brain imaging revealed minimal structural abnormalities. The second patient presented predominantly with behavioral disturbances and attention deficit hyperactivity disorder. Neuroimaging revealed delayed white matter maturation. Genetic analysis uncovered two distinct KMT2C novel variants. These cases emphasize the clinical diversity observed in KLEFS2 and highlight the importance of considering a genetic etiology in patients presenting with unexplained developmental delay. The identification of atypical features, such as metabolic abnormalities and dermatological findings, aids in refining the phenotypic spectrum of KMT2C related disorders, thereby supporting the need for thorough clinical and genetic assessment.

Keywords: *Kleefstra syndrome type 2; KMT2C; neurodevelopmental disorder; developmental delay; genotype–phenotype correlation; lactic acidosis; hypopigmented lesions; Lebanese patients*

Introduction

Kleefstra syndrome, a rare autosomal dominant neurodevelopmental disorder, is characterized by intellectual disability, developmental delay, behavioral abnormalities, and distinctive facial features (1). The condition was initially described in association with haploinsufficiency of the EHMT1 gene, which is located on chromosome 9q34.3, resulting from either submicroscopic deletions or intragenic variants (2,3). This form is classified as Kleefstra syndrome type 1 (KLEFS1, OMIM: 610253).

A second subtype, Kleefstra syndrome type 2 (KLEFS2, OMIM: 617768), has recently been identified. It is associated with pathogenic variants in the KMT2C gene (1). While more than 100 KLEFS1 cases have been reported, KLEFS2 remains exceptionally rare, with only a limited number of patients (less than 25) described to date (4,5). Consequently, the clinical spectrum and genotype-phenotype relationships associated with KMT2C-related disorders remain partly defined.

The KMT2C gene encodes a histone methyltransferase that is involved in transcriptional regulation and chromatin remodeling (4). Functional studies have demonstrated convergence between KMT2C and EHMT1 pathways, emphasizing their shared role in neurodevelopment and in the pathogenesis of intellectual disability and autism spectrum disorders(6). Haploinsufficiency of KMT2C is believed to contribute to the neurodevelopmental phenotype observed in KLEFS2 (5).

Clinically, Kleefstra syndrome is associated with moderate to severe intellectual disability, childhood hypotonia, and characteristic craniofacial features, including brachycephaly, hypertelorism, midface hypoplasia, and a protruding tongue (7). Additional manifestations may include congenital heart defects, epilepsy, autism spectrum disorder, hearing loss, and urogenital anomalies (8). However, increasing evidence suggests that the phenotypic spectrum is broader than initially recognized. Large cohort studies have demonstrated considerable variability, including milder presentations and even cases with preserved intellectual function. This reflects how complex the relationship between genotype and phenotype can be (3).

In the context of KLEFS2, this variability appears even more pronounced. Patients typically present with global developmental delays, primarily impacting speech, as well as behavioral problems that may overlap with autism spectrum disorder and attention deficit hyperactivity disorder (9). In clinical practice, this could delay the recognition of the underlying condition. Moreover, recent studies suggest that certain individuals may exhibit atypical characteristics, such as metabolic or non-classical systemic manifestations, which are still poorly understood.

The interpretation of KMT2C variations, particularly those classified as variants of uncertain significance (VUS), presents a significant challenge in the diagnosis of KLEFS2. Establishing definitive genotype-phenotype correlations remains difficult, owing to the limited number of reported cases and the considerable phenotypic heterogeneity observed. Overlapping clinical characteristics with more prevalent neurodevelopmental disorders exacerbate this confusion and may result in an initial misdiagnosis (10).

Additionally, data on long-term clinical evolution and optimal management strategies remain limited (5). Nevertheless, early diagnosis is crucial, since it enables prompt interdisciplinary therapies that could enhance quality of life and developmental trajectories (9,10).

In this context, we report two patients with distinct KMT2C variants presenting with heterogeneous clinical features. Through this case series, we aim to expand the phenotypic spectrum of KLEFS2, contribute to the interpretation of KMT2C variants, particularly variants of uncertain significance, and highlight the diagnostic challenges and clinical variability associated with this rare disorder.

Case Presentation

Case 1

A male patient was first evaluated at the age of 4 years for developmental delay, predominantly affecting speech and language. He was born at term to non-consanguineous parents without any perinatal difficulties. No family history of neurodevelopmental disorders is noted.

Early developmental milestones were partially achieved, with a normal motor acquisition of the gait, and first words at 11 months of age and normal improvement until 14 months of age , then it was followed by regression at approximately 19 months, during which previously acquired speech was lost.

At presentation, the patient showed a significant delay in expressive language, with a limited vocabulary. Despite speech therapy, the patient babbled and said a basic simple identical syllables words. Auditory evoked potentials were done before and showed normal results.

On physical examination, head circumference was above the 97th percentile for age. Dermatological examination revealed a large hypopigmented lesion following the dermatomes of the right chest and abdomen. Neurological examination was otherwise unremarkable, with normal tone, gait, and preserved reflexes. The patient maintained good eye contact and interaction. Intermittent episodes of gaze fixation were reported.

Initial metabolic investigations showed lactic acidosis, with a lactate level of 55.02 mg/dL (6.1 mmol/L; reference < 2.2 mmol/L) and and pyruvate levels (2.4 mg/dL; 272.64 µmol/L; reference 34-80 µmol/L). These abnormalities persisted on repeated separate testing for the following 12 months. Additional laboratory investigations, including plasma amino acid, urine organic acid analyses, ammonia, liver enzymes, renal function, electrolytes, and creatine phosphokinase, were within normal limits.

Brain MRI demonstrated minimal bilateral frontal bossing and mild dilatation of the posterior lateral ventricles. The brain parenchyma was otherwise normal, with age-appropriate myelination and no abnormal signal intensities. Magnetic resonance spectroscopy was normal. There was no epileptiform activity on the EEG.

The patient exhibited global developmental delays in speech and psychomotor development. There was an impairment of expressive and receptive speech, as well as non-verbal communication skills. A multidisciplinary approach was initiated, including speech therapy, psychomotor therapy, and special educational assistance. Over time, he demonstrated developmental progress, including the expansion of his vocabulary, acquisition of short phrases, and improvement in his ability to socially interact. He was able to recognize colors, count in different languages, and interact more effectively with his environment. However, there were difficulties in articulation, attention, and behavioral issues such as hyperactivity, stereotypy, and inappropriate behaviors.

Whole exome sequencing identified a novel heterozygous missense variant in the KMT2C gene (c.10874C>T), resulting in a p.(Pro3625Leu) substitution in exon 43.

During a 10 years follow-up into adolescence, the patient continued to demonstrate developmental delay, but showed improved behavioral stability and social interaction. He demonstrated improved ability to communicate in short phrases, but had significant difficulties in reading and writing. The main persisting behavioral features included persistent hyperactivity and stereotypies. Treatment with, risperidone, methylphenidate and aripiprazole showed no benefits in improving the patient's behavior. But the patient demonstrated improved behavioral stability on topiramate and atomoxetine, which reduced his hyperactivity and improved his interaction. Physical examination remained unremarkable.

After a 10 years follow up the patient is able to produce 2-3 words appropriate sentences, socially independent at home, can execute simple orders, and perform regular daily activities, the main challenge remains the behavioral aspect.

Case 2

A male patient was evaluated for the first time at 6 years of age, he presented for speech and cognitive delay that was first noted at 2 years of age. The patient had no reported history of perinatal complications. Family history and pedigree analysis did not reveal any similar neurodevelopmental disorders, consanguinity, or any known genetic conditions. He followed normal motor milestones, said his first words at 1 year of age, and showed at steady improvement until 18 months of age and then started a severe regression until losing all his language acquisitions at 2 years of age. Intensive therapy sessions were started, speech and psychomotor therapy, in an inclusive educational system.

Physical examination was unremarkable, with normal neurological findings. No dysmorphic features or cutaneous abnormalities were reported.

Brain magnetic resonance imaging revealed delayed white matter maturation, without additional structural abnormalities. Cardiac evaluation, including echocardiography and Doppler studies, demonstrated overall normal cardiac structure and function, with mild left ventricular dilation, a small patent foramen ovale with left-to-right shunt, and trace tricuspid regurgitation. No significant congenital heart disease was identified.

A genetic etiology was strongly suspected given the persistence of symptoms despite adequate ADHD therapy and the presence of global developmental delay. Whole exome sequencing identified a novel variant in the KMT2C gene (c.12673C>T; p.Arg4225*), consistent with a diagnosis of autosomal dominant Kleefstra syndrome type 2.

The patient was enrolled in a specialized educational setting with a shadow teacher. While maintaining reading and writing skills, the patient had a significant developmental delay that predominantly impacted speech and severely limited expressive language. Cognitive performance was inconsistent, with slow calculating ability but relatively preserved literacy skills. By the age of 6 years the patient had clear targeted speech, was able to write his name and around 30 words in Arabic, and was able to write two words sentences in English. The main challenge remained the attention deficit and the hyperactivity that was treated at first by risperidone, Atomoxetine and methylphenidate. Despite treatment, the patient continued to exhibit significant behavioral difficulties, encompassing both agitation and poor academic performance. Upon subsequent assessment, the patient exhibited ongoing behavioral instability, characterized by episodes of agitation and limited improvement under pharmacological treatment. Furthermore, developmental delay persisted, specifically impacting speech and communication, despite preserved basic academic skills. A noted behavioral improvement was observed when given a treatment of a low dose of topiramate.

Discussion

Kleefstra syndrome type 2 is a rare and incompletely characterized neurodevelopmental disorder, with a limited number of reported cases. Thus, this restricts the current understanding of its clinical and genetic spectrum (4,5). In this study, we describe two patients with distinct KMT2C variants who exhibited a range of clinical characteristics, highlighting the condition's heterogeneity and adding to its expanding characterization. To our knowledge these are the first patients with KMT2C mutations reported in the Lebanese population.

The KMT2C gene encodes a histone methyltransferase involved in chromatin remodeling and transcriptional regulation. Through its role in epigenetic control of gene expression, KMT2C contributes to neuronal development, synaptic function, and cellular differentiation. Disruption of these processes is therefore expected to result in neurodevelopmental impairment, as observed in both patients (4,6).

They both demonstrated core characteristics, such as global developmental delay and significant expressive language impairment, that are typical of KLEFS2 cases that have been previously documented (9,10). However, their clinical presentations differed significantly, highlighting the heterogeneity of KMT2C related disorders.

The first patient presented with early developmental regression, macrocephaly, and persistent lactic acidosis. While neurodevelopmental impairment is a recognized feature of KLEFS2, metabolic abnormalities are not typically considered part of its classical presentation (1). The persistence of lactic acidosis, in the absence of an identifiable primary metabolic disorder, raises the possibility of an association with the condition. However, a direct causal relationship cannot be established, and this finding may represent either an atypical feature or a coincidental observation. In addition, the presence of a large hypopigmented cutaneous lesion is an uncommon finding that has not been commonly reported in association with Kleefstra syndrome type 2. Although no direct causal link can be confirmed, this observation may contribute to refining the clinical spectrum of KMT2C-related disorders. Careful documentation of such atypical features is important in rare genetic conditions, where each additional observation can help improve phenotypic characterization.

The second patient, on the other hand, exhibited primarily behavioral symptoms and was first diagnosed with attention deficit hyperactivity disorder. Despite his literacy abilities, he had considerable expressive language impairment and ongoing developmental delays. This clinical presentation highlights a diagnostic challenge, since KLEFS2 might first resemble more common neurodevelopmental diseases, possibly delaying genetic detection (9,10). The persistence of symptoms despite proper ADHD medication highlights the importance of looking for an underlying genetic etiology in atypical or treatment-resistant individuals.

Neuroimaging findings also differed between the two patients. While the first patient showed minimal structural abnormalities, the second demonstrated delayed white matter maturation. Although nonspecific, these findings may reflect delayed neurodevelopment rather than a distinct structural abnormality.

From a genetic standpoint, both patients carried rare KMT2C variants, including a missense variant and a truncating variant.

The distinction between variant types further illustrates the complexity of variant interpretation. Although truncating mutations are typically thought to be linked to loss of function, it is yet unclear how certain KMT2C mutations affect clinical outcomes. This emphasizes the ongoing challenge of establishing genotype-phenotype correlations in rare disorders (5).

The findings of this study have important clinical implications. For instance, early molecular diagnosis through whole exome sequencing enables appropriate multidisciplinary management, including developmental therapies and behavioral interventions. It also facilitates genetic counseling and improves diagnostic accuracy, particularly in patients with atypical presentations or poor response to standard therapies.

The response to topiramate treatment is yet to be explored, the clear underlying physiopathology should be studied on a larger sample, a possible explanation can be the blocking effect of topiramate on methyltransferase genes in case of abnormal de novo methyltransferase activity consequent to the KMT2C mutation (11).

These findings suggest the phenotypic heterogeneity linked to KMT2C-related disorders, and emphasize the challenges involved in establishing distinct and clear genotype-phenotype relationships. The coexistence of classical neurodevelopmental features with atypical findings, including metabolic abnormalities and dermatological manifestations, further reflects the complexity of this condition.

The continued accumulation of clinically well-characterized cases will be required to further identify and define the full spectrum of Kleefstra syndrome type 2.

Conclusion

In conclusion, this case series highlights the clinical variability of Kleefstra syndrome type 2, as well as the need to consider a genetic etiology in children with unexplained developmental delay. Moreover, the identification of rare KMT2C variants, as well as atypical traits such as metabolic abnormalities and dermatological findings, help to refine the disorder's phenotypic spectrum and emphasize the importance of comprehensive clinical and genetic evaluation.

Conflict of Interest

None of the authors has a conflict of interest with the material presented in this paper.

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