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First reported case of de Novo claes-jensen syndrome (CJS) in Palestine: diagnostic challenges and genetic insights

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Abstract

Background Claes-Jensen syndrome (CJS) is a rare X-linked intellectual disability caused by mutations in the KDM5C gene, encoding a histone demethylase involved in chromatin remodeling and neurodevelopment. Males with hemizygous mutations in KDM5C present with intellectual disability, dysmorphism, and neurodevelopmental delays. Mutations, either maternally transmitted or de novo, account for 0.7-2.8% of X-linked intellectual impairments. This case reports a rare de novo variant in the KDM5C gene in a Palestinian male patient, contributing to the limited literature on this condition.

Case presentation We present a 2-year and 10-month-old Palestinian male with developmental regression following an acute viral illness at 22 months. This included the loss of the ability to walk, developmental delays, and persistently elevated lactic acid. Genetic testing, including trio-based whole-exome sequencing, identified a de novo KDM5C mutation (c.2827 C > T p.Arg943), confirming the diagnosis of Claes-Jensen syndrome. Neuroimaging showed faint hyperintensities in the posterior periventricular white matter, suggestive of dysmyelination.

Conclusion This case highlights the diagnostic challenges of CJS and the importance of genetic testing in neurodevelopmental disorders. Early recognition aids in symptomatic management and improves clinical understanding of this rare condition. Our report adds new insight into the clinical spectrum of CJS and emphasizes the need for heightened awareness among clinicians.

Keywords Claes-Jensen syndrome, De Novo variants, KDM5C gene, Intellectual disability

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Background

Claes-Jensen syndrome (CJS) is a rare X-linked intellectual disability caused by mutations in the KDM5C gene, which encodes a lysine (k)-specific demethylase 5 C. The KDM5C gene plays a crucial role in chromatin remodeling and gene expression regulation by demethylating histones. While most heterozygous female carriers remain asymptomatic, hemizygous males exhibit facial dysmorphism and intellectual impairment [1].

Located at Xp11.22, the KDM5C gene encodes a 1560-amino acid protein that functions as a key epigenetic regulator, essential for cognitive development through dose- and time-dependent mechanisms. Mutations in KDM5C lead to moderate-to-severe intellectual disability, short stature, dysmorphic features, seizures, and spasticity in males. Carrier females may show milder symptoms, such as intellectual disability and spasticity [2]. Mutations in KDM5C account for 2.8–3.3% of X-linked intellectual disabilities, which affect 1–3% of the general population [3].

We report the first documented case of Claes-Jensen syndrome in Palestine, adding to the scarce literature on this rare X-linked disorder. The patient, a 2-year-old male, exhibited developmental regression following a viral illness at 22 months, accompanied by persistently elevated lactic acid. Whole-exome sequencing (WES) with trio analysis revealed a de novo KDM5C mutation, confirming the diagnosis. This case not only underscores the diagnostic complexity of CJS but also highlights the need for greater clinical awareness and research into its presentation and management. By shedding light on this rare condition, we aim to bridge gaps in knowledge and enhance early recognition in diverse populations.

Case presentation

We present the case of a 2-year and 10-month-old male child from Palestine who developed developmental regression following an acute viral illness at 22 months of age. The illness was characterized by recurrent diarrhea, vomiting, fever, generalized weakness, weight loss, and poor weight gain since the age of one. Notably, the patient lost the ability to walk following this illness.

Developmental milestones were delayed from an early age, with the child sitting unsupported at 15 months, walking at 18 months, transferring objects between hands and using a two-finger grasp by 24 months, and speaking only "Ma," "Da," "Mama," and "Dada." These findings suggest developmental regression following the viral illness in the context of pre-existing developmental delay.

Pregnancy was spontaneous, with complications including Coronavirus Disease 2019 (COVID-19) infection at 7 months gestation and hypertension in the later stages. The child was delivered at 38 weeks via cesarean section due to maternal hypertension, with a birth weight of 3700 g, and no immediate neonatal concerns.

At presentation, the patient weighed 10 kg, had a head circumference of 48 cm, and a length of 76 cm. Physical examination revealed no dysmorphic features. Neurological findings included mild increased tone in both ankles, hyperreflexia (deep tendon reflexes graded 3+), and normal axial tone. Pulmonary, cardiac, abdominal, musculoskeletal, and genital examinations were all normal. Laboratory investigations showed microcytic red blood cells (RBCs) and persistently elevated lactic acid, raising concerns for a metabolic disorder, particularly mitochondrial dysfunction.

Echocardiography demonstrated normal cardiac structure and function, while (Fig. 1), brain magnetic resonance imaging (MRI) revealed faint hyperintense signals in the posterior periventricular white matter on T2/FLAIR imaging, suggestive of dysmyelination, but no structural abnormalities or midline shifts. Urine Gas chromatography-mass spectrometry (GC-MS) was non-diagnostic, although alkaline level was elevated at 643 µmol/L.

A WES with trio analysis identified a de novo variant in the KDM5C gene (NM_004187.5X:5322602 c.2827 C > T p.Arg943), confirming the diagnosis of CJS.

Discussion

CJS is a rare X-linked intellectual developmental disorder resulting from mutations in the KDM5C gene, which encodes a histone lysine demethylase involved in chromatin remodeling and histone modification—critical processes for normal neurodevelopment [1]. Affected males with mental retardation, X-linked, syndromic, Claes-Jensen type (MRXSCJ) often exhibit significant clinical heterogeneity, including delayed intellectual development, short stature, and hyperreflexia [4]. Approximately 0.7–2.8% of X-linked intellectual impairment cases can be attributed to maternally transmitted or, less frequently, de novo pathogenic mutations of the KDM5C gene [5].

In our case, WES was performed using the Illumina NOVASEQ 6000 platform, with bioinformatics analysis conducted via the DRAGEN pipeline, using the hg19 reference genome. This revealed a hemizygous c.2827 C > T nonsense variant in KDM5C (chrX:53226022), resulting in a premature stop codon (p.Arg943*). This variant was classified as likely pathogenic based on the ACMG/AMP 2021 guidelines, fulfilling the following criteria:

PVS1(very strong): A null variant (nonsense) in a gene where loss-of-function is a well- established disease mechanism (confirmed via AutoPVS1),

PM2 (absent in population databases such as gnomAD and ExAC), and.

PP5 (previously reported in a patient with overlapping phenotype [6].

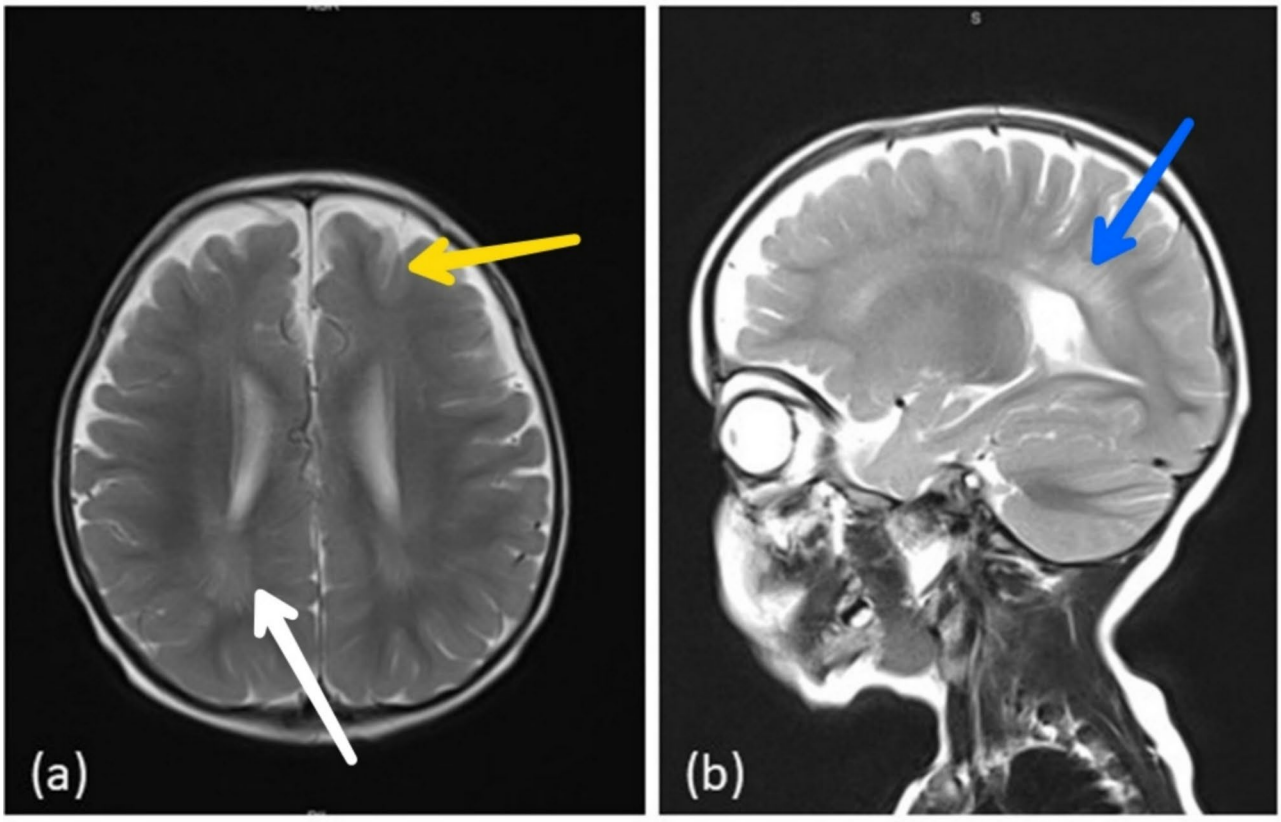

Fig. 1 Axial (**a**) and sagittal (**b**) T2-weighted MRI images demonstrating faint, confluent high signal intensities in the periventricular and deep white matter, predominantly affecting the bilateral posterior periventricular regions (white arrow), with relative sparing of the subcortical U fibers (yellow arrow). Milder involvement is noted in the anterior periventricular region (blue arrow)

Furthermore, in silico analysis tools such as MutationTaster predicted the variant to be disease-causing, and its classification was supported by the gene's high intolerance to loss-of-function (pLI = 1). The variant was not detected in the mother, confirming its de novo origin, which aligns with the known inheritance pattern in CJS.

The KDM5C mutation identified in our patient appears to be a rare de novo variant. In this case, the patient presented with hyperreflexia and spasticity, consistent with the clinical phenotype typical of CJS. Brain MRI showed faint hyperintensities in the posterior periventricular white matter, suggestive of demyelination, aligning with the established role of KDM5C in brain development. These findings further support the link between structural brain abnormalities and white matter changes in individuals with KDM5C mutations [7].

In this case report, an acute viral illness preceded the onset of developmental regression. While viral infections may act as nonspecific physiological stressors that exacerbate the clinical presentation of underlying neurogenetic disorders, there is no established evidence suggesting a direct etiological link between such infections and KDM5C-related Claes-Jensen syndrome. It is therefore more likely that the developmental regression observed in our patient reflects the natural course of the disorder, irrespective of the preceding illness. However, the temporal association may obscure the recognition of a genetic etiology and thus complicate the diagnostic process. This highlights the importance of considering both environmental and genetic factors in the evaluation of developmental disorders. Further studies are needed to elucidate how external triggers may influence the phenotypic expression or clinical trajectory of single-gene neurodevelopmental syndromes.

Recent advancements in genetic testing have shifted from Chromosomal Microarray Analysis (CMA), with diagnostic yields of 16–28%, to WES and Whole Genome Sequencing (WGS), which offer higher diagnostic yields and are now recommended as first- or second-tier tests. Trio Exome Sequencing has demonstrated diagnostic yields of 50–70% in cases of severe intellectual disability [8].

In our case, WES confirmed the diagnosis of CJS by identifying a characteristic mutation. This supports the growing evidence of WES's efficacy, particularly in complex syndromic intellectual disabilities. Furthermore, specific clinical features such as developmental delay, short stature, elevated lactic acid, and increased muscle

tone provided phenotypic clues that helped interpret the genetic findings. These observations emphasize the importance of deep phenotyping in complementing genetic data. While no targeted therapies are available for intellectual disabilities linked to KDM5C mutations, symptomatic management remains the primary approach [9, 10].

Conclusion

CJS is a rare X-linked intellectual developmental disorder, and its occurrence with de novo variants makes it even rarer. This article aims to provide further insight into this uncommon condition and emphasizes the importance of considering it in the differential diagnosis of neurodevelopmental symptoms. Early recognition of such rare and serious disorders is crucial for accurate diagnosis and management.

Abbreviations

CJS	Claes-Jensen syndrome
KDM5C	Lysine (K)-Specific Demethylase 5 C
WES	Whole-exome sequencing
COVID-19	Coronavirus Disease 2019
RBCs	Red blood cells
MRI	Magnetic Resonance Imaging
GC-MS	Urine Gas chromatography-mass spectrometry
MRXSCJ	Mental Retardation, X-Linked, Syndromic, Claes-Jensen Type
CMA	Chromosomal Microarray Analysis
WGS	Whole Genome Sequencing
DRAGEN	Dynamic Read Analysis for GENomics
ACMG/AMP	American College of Medical Genetics and Genomics/ Association for Molecular Pathology
PVS1	Pathogenic Variant, Strong Evidence
PM2	Absent in population databases
PP5	Previously reported in a patient with a similar phenotype
pLI	Probability of Loss-of-Function Intolerance

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Author contributions

M.S contributed to writing the case presentation and abstract, as well as editing and reviewing the manuscript; S.A, I,A wrote the discussion and reviewed references; L.J wrote the background; A.A wrote the abstract and conclusion; H.A interpreted the radiological images; R.M supervised the study and assisted in gathering information from the family; all authors reviewed and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

Consent to publish

Written informed consent for publication of this case report and any accompanying images was obtained from the patient's legal guardians.

Competing interests

The authors declare no competing interests.

Clinical Trial Registration

Not applicable.

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