# Kleefstra Syndrome with Severe Sensory Neural Deafness and *De Novo* Novel Mutation

Huma Arshad Cheema, Nadia Waheed and Anjum Saeed

*Department of Pediatric Gastroenterology and Hepatology, Children Hospital and Institute of Child Health, Lahore, Pakistan*

## ABSTRACT

Kleefstra syndrome is a rare inherited neuro-developmental condition characterised by facial dysmorphism, microcephaly, hypotonia, developmental delay, and intellectual disability. It is a rare syndrome; and less than 100 cases with different genetic mutations are reported so far. We report an eight-month baby boy with Kleefstra syndrome type 2 due to a novel *de novo* pathogenic mutation in the *KMT2C* (Lysine methyltransferase 2C) gene.

**Key Words:** *Kleefstra syndrome, KMT2C gene, Neurodevelopmental disorder, Deafness.*

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## INTRODUCTION

In 2012, Kleefstra *et al.* reported a syndrome characterised by psychomotor delay, intellectual disability, childhood hypotonia, and distinctive dysmorphic facies with underlying genetic defect. Hence, the condition was named as Kleefstra syndrome (KS).[1] Around 100 cases have been reported in literature from different parts of the world with diverse clinical manifestations and genetic variants. Genetic mutations in the euchromatin histone methyltransferase 1 (*EHMT1*) gene and lysine methyltransferase 2C (*KMT2C*) are responsible for KS type 1 and type 2, respectively. Type 1 is more common (75% of all cases) than type 2.

The clinical phenotype includes distinctive facial features like midface hypoplasia, brachycephaly, upward slanting palpebral fissures, synorphy, hypertelorism and an anteverted lower lip in addition to other general features of psychomotor delay, intellectual disability and generalised hypotonia.[2] We report a case of KS in a eight-month male child with severe sensory neural deafness due to novel mutation, which has never been described before in KS.

## CASE REPORT

An eight-month boy was referred to our Pediatric Department with history of seizures since neonatal life. He was born full-term to consanguineous parents with uneventful ante- and post--natal history. He has an elder brother with developmental delay and a normal, healthy six years sister. There was also history of psychomotor retardation in a second degree cousin (Figure 1A).

He remained well for the first 24 hours after birth with good oral intake; but during the second post-natal day, his attendant observed abnormal facial movements and right upper limb twitching lasting a few seconds. All metabolic profile blood tests including glucose, serum calcium, magnesium, liver and renal function tests were normal; and he was discharged home. On third post-natal day, he had an episode of generalised clonic seizures lasting a few minutes; and as a result, he was readmitted to the hospital. Metabolic, septic and cerebrospinal fluids (CSF) examinations were all normal. Electroencephalogram (EEG) revealed prolonged periods of burst suppression. His oral intake was adequate without any vomiting. There was no evidence of respiratory distress and no abnormality of urinary output or bowel habits. His developmental milestones were delayed including motor, social smile and eye contact. He could achieve partial neck holding at 7 months of age with a tilt to the left. He was initially started on a single anti-epileptic drug, which provided partial control of seizures and another anti-epileptic was added later on.

On examination, there was an obvious facial dysmorphism in the form of hypertelorism, brachycephaly, mid-face hypoplasia, everted lower lip and head-tilt to the left side (Figure 1). His fronto-occipital circumference (FOC) was 36.5 cm (<-2SD), weight 6 kgs (-3SD) and length was 66 cm (-3SD). Central nervous system examination revealed normal tone with brisk reflexes and bilateral up-going planters (normal findings for age). He had global developmental delays and his milestones were found to drop off at 3.5 months of age.

*Correspondence to: Dr. Nadia Waheed, Department of Pediatric Gastroenterology and Hepatology, Children Hospital and Institute of Child Health, Lahore, Pakistan*
*E-mail: drnadiasalman@gmail.com*

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**Table I: Whole exome sequencing with details of mutation in the index child with Kleefstra syndrome.**

| Gene | Variant coordinates | Zygosity | In silico parameters | Allele frequencies | Type of mutation |
|---|---|---|---|---|---|
| KMT2C | Chr7(GRCh37):g.151877103_151877114del<br>NM_170606.2:c.7247_7258del<br>p.(His2416_Pro2419del<br>Exon 37 | Hetero | Polyphen:N/A<br>Align-GVGD: N/A<br>SIFT: N/A<br>Mutation Tester: N/A | GnomAD:-<br>Esp:-<br>1000g:-<br>Centomad:- | In-frame deletion |

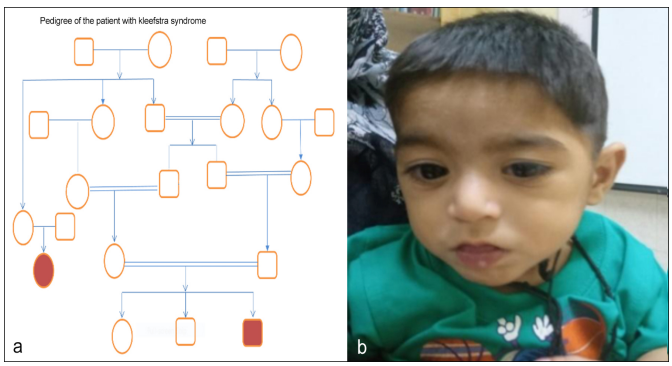


**Figure 1: (a) pedigree of the index case. (b) Dysmorphic facial features: Coarse face, flattened midface, prominent eyebrows, everted lower lip, microcephaly and thick ear helices and pedigree of patient.**

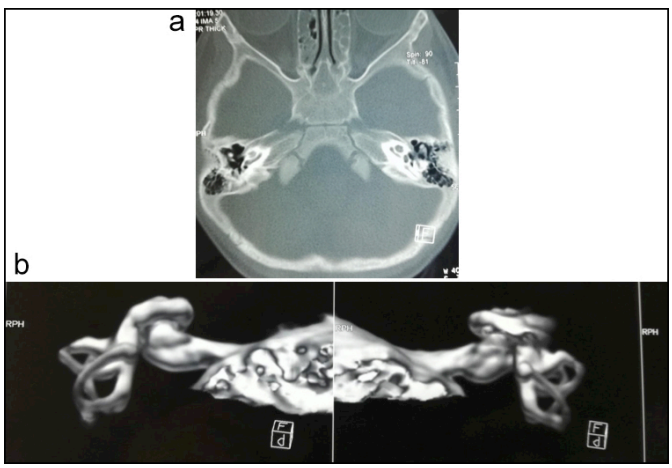


**Figure 2: (a) The middle ear cavity is well pneumatised with no significant osseous abnormality. (b) The internal auditory canals appear patent. Semi-circular canals appear normal. Cochleas have normal two and half turns bilaterally.**

Rest of systems including cardiovascular, respiratory and gastrointestinal tract were unremarkable. The laboratory parameters were within normal limits including blood gases, liver and renal functions. Complete blood count (CBC) and serum electrolytes were also unremarkable, in addition to normal ammonia and serum lactate. Magnetic resonance imaging (MRI) of brain showed normal ventricular system, cortex and white matter, except for thinning of corpus callosum along with splenium. Mucosal thickening was noted in ethmoidal sinuses but mastoid air cells were well pneumatised bilaterally. The internal auditory canals and semi-circular canals appeared patent and normal as well as cochlea have normal two and half turns bilaterally. The 7$^{th}$ and 8$^{th}$ cranial nerve complexes and cochlear divisions were also normally visualised and seen on oblique multi-planar reconstruction (MPR) image of fast imaging employing steady-state acquisition (FIESTA) sequences. The middle ear cavity was well pneumatised with no significant osseous abnormality, as shown in Figure 2(A and B). Brain-stem evoked response audiometry (BERA) revealed bilateral profound sensory neural deafness as shown in Figure 3(A and B). Whole exome sequencing identified a novel *de novo* heterozygous pathogenic variant in *KMT2C* gene, which confirmed the diagnosis of autosomal dominant KS, type 2, as shown in Table I.

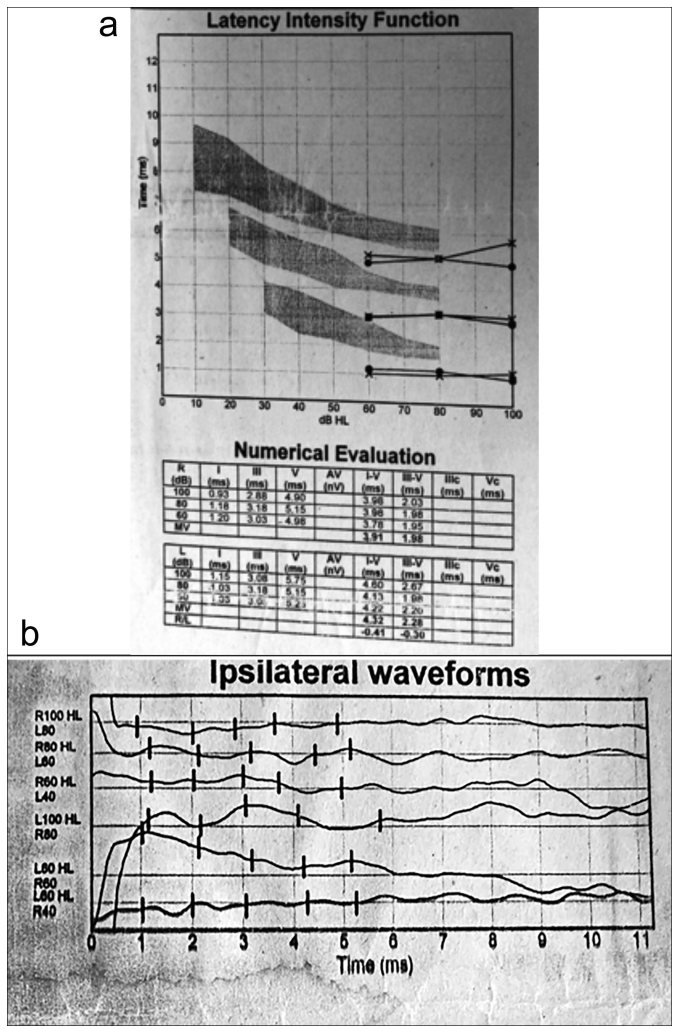


**Figure 3: (a, b): Brainstem evoked response audiometry (BERA) of the same child showing the profound sensory neural deafness.**

## DISCUSSION

KS (OMIM 606833) is a rare disorder of psychomotor retardation and intellectual disability with distinctive facial features. To the best of our knowledge, this is first report from Pakistan about KS. This syndrome was first described in a girl with delayed psychomotor development and low intelligent quotient (IQ) of 35. She achieved independent walk at age of 19 months, but no verbal communication. Later, she

developed hyperactivity and aggressiveness. At 15 years of age, she was short-statured, and microcephalic with dysmorphic features.[3] Our index case had similar presentation with global developmental delay and psychomotor retardation.

Distinctive facial features are characteristics of KS, as described by Koemans *et al*.[4] They reported five unrelated patients with KS type 2 syndrome with typical dysmorphic features. The same dysmorphism was present in our index child. In addition to dysmorphism and global developmental delay, some children present with seizures, as described in the same report. Our index child had intractable seizures, which could not be controlled on monotherapy; and second drug had to be added to control the convulsions. They also reported some other features like autism in one of them and childhood hypertonia with scoliosis in three patients. None of these symptoms were present in our case.

Recently, Faundes *et al.* reported three unrelated patients' typical features as dysmorphic facial features with psychomotor delays. In addition to typical characteristics, he also described duplicated thumb and hydrocephalus with Dandy-Walker malformation and hypoplasia of the cerebellar vermis in two children.[5] Our case had no such findings.

Recently, otopathology has been described in KS revealing that 20-30% children develop hearing loss.[6] In contrast to this study, our patient did not have any abnormalities of middle ear. Our index child had no response to commands when called and other stimuli, which led to investigations for hearing, which showed severe sensory neural deafness.

The sensory neural deafness has not been reported in any of cases of KS, previously. This severe sensory neural deafness might be the reason for his speech delay.

Various *de novo* pathogenic variants have been described in the literature, like our index case. Both parents were normal without carrying any genetic mutation; and siblings also had no mutations. Such children can appear normal at birth and can present later in life, and others may have immediate signs from birth, as in our case, who had seizures soon after birth.[7] Symptomatic control with anti-epileptic drugs, nutritional care and occupational therapy may help in these children. For the hearing impairment, devices like Cochlear implants are useful adjunctive therapy. In our case, convulsions were well controlled with good oral intake and we advised Cochlear implant with the hope that this will help in his speech issues. Parents are counselled about the nature of disease and offered pre-natal screening for future pregnancies.

KS is a rare neuro-developmental disorder with diverse clinical presentations. Distinctive facial features, psychomotor retardation and global developmental delays are the prominent features helpful in narrowing the diagnosis. The case described in this paper adds to the existing knowledge-base by describing a novel *de novo* mutation associated with KS, found in a male child in Pakistan.

**PATIENT'S CONSENT:**
Informed consent was obtained from patient's parents to publish the data concerning this case report.

**CONFLICT OF INTEREST:**
The authors declared no conflict of interest.

**AUTHORS' CONTRIBUTION:**
NW: Compiled all data, write-up and literature search.
AS: Helped in searching literature.
HAC: Helped in proofreading.

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