# Developmental Delay and Epilepsy Without Gigantism: An Unusual Presentation of Soto's Syndrome Due to A Novel Mutation in the NSD1 Gene

A 2-year-old girl presented with developmental delay and seizures for 3 months of age. She was born to non-consanguineous parents with a normal perinatal period and normal birth weight (3.3 kg). She had more delay in attainment of language, and social milestones, as compared to gross and fine motor milestones. She was able to walk without support, could speak two monosyllable-words, and attained stranger anxiety recently. She had unprovoked generalized tonic-clonic seizures for 3 months of age, 1–2 episodes/month, lasting for 2–5 minutes, and could be controlled with levetiracetam. An examination revealed normal weight (13 kg), length for age (86 cm), weight for length, and normal occipitofrontal circumference for age (50 cm) (all between 0 to 2Z scores). Arm span/height ratio (1.01), sitting/standing height ratio (0.614), and hand length (4 cm) were within normal limits. The height of the father and mother were 176 cm and 164 cm, respectively and the head circumference of the father and mother were 56 cm and 55 cm, respectively. The child did not have any facial dysmorphism, body asymmetry, or any other congenital anomalies.

Her magnetic resonance imaging of the brain was normal, and electroencephalogram showed frequent bilateral frontotemporal epileptiform discharges. Whole-exome sequencing detected a novel heterozygous nonsense pathogenic variation in exon 7 of the *NSD1* gene (c. 3982A > T, p.Lys1328Ter), suggesting a diagnosis of Soto's syndrome. Sanger sequencing confirmed the presence of this mutation, and both the parents were negative for the variant. X-ray of the left wrist [Figure 1] was done in absence of other suggestive clinical features to detect bone age which was found to be advanced (6–7 years).

Soto's syndrome is a rare autosomal dominant disorder with prevalence being 1 in 14,000 live births. It usually presents with overgrowth in stature or various body parts, developmental/delay/intellectual disability, and often a distinctive facial appearance (large dolichocephalic head, down slanting palpebral fissures, a broad forehead, long narrow chin).[1] Hypotonia, delayed language and motor development, incoordination, behavioral abnormalities, intellectual disability, and seizures are neurological manifestations seen in these children. Previous reports have suggested that around 9-50% of the children with Soto's syndrome develop febrile and afebrile seizures, but isolated presentation with seizures predominantly is rare with Soto's syndrome. Apart from febrile seizures, these children have been reported to have generalized tonic-clonic (GTCS), absence seizure, myoclonic seizure, and focal seizures also. Among generalized seizures, GTCS is the commonest semiology seen in 47% of the cases with generalized epilepsy. Among cases with focal seizure, temporal lobe semiology is most commonly seen in around 40% of cases. Clinical symptomatology of temporal lobe seizures included gustatory, olfactory, or auditory hallucinations, automatisms, fear, auras like abdominal aura with/without behavioral arrest, deja vu, or jamais vu like sensations. Predominant elcetroencephalogram abnormalities included focal or multifocal discharges among which discharges from temporal lobe electrodes were most common. Valproic acid, oxcarbazepine, carbamazepine, lamotrigine, levetiracetam, and topiramate at standard doses are effective for seizures in Soto's syndrome. In a series, 2 out of 19 children only required polytherapy for epilepsy.

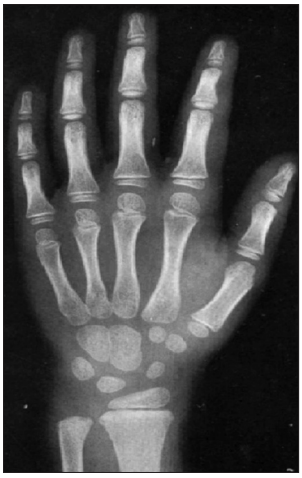

**Figure 1:** X-ray wrist of left hand at 2 years of age (antero-posterior view) showed seven carpal bones suggestive of advanced bone age (6–7 years)

Our case has an unusual presentation as she had normal weight, height, and head circumference at the time of presentation, although the possibility of developing overgrowth features later in life cannot be ruled out at this point. A similar presentation in a 3-year-old girl has been presented by Gowda *et al*.[2] However, that case presented without seizures and the presenting symptoms were mainly developmental delay and behavioral abnormalities. Moreover, the birth weight of our case was normal, although the bone age was advanced, corroborating with the findings of Soto's syndrome. A minority of the cases of Soto's syndrome have been reported to have such presentation with growth parameters not crossing the 97$^{th}$ percentile for age and gender.[1] Otherwise, macrocephaly and gigantism are usually considered as some of the clinically useful diagnostic clues for Soto's syndrome.

Nicita *et al*.[3] have reported long-term follow-up of 19 patients with Soto's syndrome who had either febrile seizure and/or epilepsy during childhood, although all of them had overgrowth features. Half of the patients with

Soto's syndrome who had febrile seizures developed epilepsy later.[4,5] Clinicians need to suspect Soto's syndrome in children with developmental delay and epilepsy, even without the characteristic facial appearance and overgrowth features. In such cases, often advanced bone age can be used as a surrogate marker for aiding in early diagnosis. Advanced bone age is seen in about 75% of cases with Soto's syndrome and often can serve as a useful diagnostic clue in cases without other overgrowth features. In such cases with females, early menarche has also been reported.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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**Submitted:** 12-Mar-2021 **Revised:** 31-Mar-2021
**Accepted:** 06-May-2021 **Published:** 29-Jun-2021



**DOI:** 10.4103/aian.AIAN_209_21