

## Pseudo Hypsarrhythmia: An Early Marker of Angelman Syndrome

### CASE REPORT

An 18-month-old girl presented with concerns of language delay and recurrent seizures from the age of 12 months. She was the second born to a nonconsanguineous couple and had an uneventful perinatal period. Her development was age-appropriate except in the language domain. She recognized words for common items like “cup,” and listened when spoken to, but her expressive language was restricted to gurgling sounds and babbling. Her seizures were brief, generalized tonic, and were associated with a short period of postictal drowsiness. Grinding of teeth was also noted. The seizure frequency had gradually increased to 4–5 episodes per week over the last 6 months, and the parents had noticed the appearance of generalized tremulousness and lack of any new milestones. At 18 months of age, she was able to take a few steps by holding on to furniture, pick up small objects, and wave bye-bye. Her speech was unclear, she used gestures to communicate and was still babbling.

On examination, she was easily excitable and had frequent unprovoked episodes of laughter. Her mouth was constantly open, and she had a protruded tongue. She also exhibited abnormal, involuntary, brief, non-stereotypic uncoordinated, jerky movements of arms and legs. Her occipitofrontal head circumference was 42.5 cm suggestive of microcephaly (−3.05 Z score by WHO growth charts). Her neurological examination revealed mild generalized hypotonia. Her magnetic resonance imaging of the brain was unremarkable [Figure 1]. Her electroencephalography (EEG) at 1 year of age showed runs of high amplitude generalized irregular delta waves with multifocal epileptiform discharges suggestive of hypsarrhythmia [Figure 2]. A repeat EEG at 18 months of age showed rhythmic delta activity more pronounced in the frontal region with superimposed notched appearance on the descending phase of slow wave [Figure 3]. Her karyotype was normal (46, XX). Fluorescence *in situ* hybridization confirmed the diagnosis of Angelman syndrome (AS) by microdeletion of 15q11–q13 in all

100 cells using Vysis Prader-Willi/Angelman region DNA probe LS1 small nuclear ribonucleoprotein polypeptide N. A neurorehabilitative program was initiated, and antiepileptic drug titration was done to control epilepsy.

### DISCUSSION

AS is a rare neurogenetic disorder with a prevalence of 1:10000–1:40000.<sup>[1]</sup> The consistent clinical picture comprises of severe intellectual impairment, easily excited behavior phenotype with frequent laughters, balance, and speech impairment.<sup>[2]</sup> Fascination with water and prominent microbrachycephaly with protruded tongue are clinical hints. One of the problems for the early diagnosis is that the complete phenotypic expression becomes evident only after 3 to 4 years. Epilepsy in AS typically develops at 1–3 years of age with onset ranging from 1 month to 20 years. Most frequent seizure types are atypical absence, generalized tonic-clonic, and myoclonic seizures.<sup>[3]</sup> Vendrame *et al.*, in their prospective study of 115 children with AS, identified age as robust predictor of seizure onset, with the odds of developing seizures increasing by a factor of 1.29 for every year of life.<sup>[4]</sup> The electroencephalographic patterns, although are not pathognomonic, are sufficiently characteristic for the diagnosis. Excessive hypersynchronous electrical activity over the thalamocortical and hippocampal networks secondary to misregulation of gamma-aminobutyric acid inhibitory system is the proposed mechanism of epilepsy in AS.<sup>[5]</sup> The typical EEG patterns are, in general, detected early in the course of syndrome, even before the onset of epilepsy. Another interesting facet is the lack of difference in EEG findings in patients with and without epileptic seizures.

Boyd *et al.* first described three unequivocal patterns of electrophysiological activity in AS as follows: (a) prolonged rhythmic theta 4–6 s theta activity more evident in the centroparietal region; (b) generalized rhythmic 2–3 s delta

activity more pronounced in the anterior cortical region; and (c) spikes mixed with rhythmic delta/theta activity in the posterior region facilitated by passive eye closure.<sup>[6]</sup>

Interindividual and intraindividual variations in the most common delta pattern were reported by Valente *et al.* in 47 EEGs of 23 patients and included hypsarrhythmia-like variant, notched variant, triphasic-like variant, and slow variant.<sup>[7]</sup> The association of hypsarrhythmia-like pattern with AS, as in the index case, is poorly recognized and has been reported in only a handful of cases.

The first description of hypsarrhythmia in AS was reported in Mayo *et al.*, in 1973, in a 32-month-old toddler with global delay.<sup>[8]</sup> Since then, hypsarrhythmia variant has been limited to less than 20 cases worldwide. Valente *et al.* recognized three EEGs with similar pattern in two children at 4 months, 14 months, and 15 months, respectively, in a review of serial EEGs of 26 patients. Vendrame *et al.* conducted the largest prospective study to delineate the EEG features in a large cohort of 160 children followed longitudinally in the Angelman Natural history study. The authors had reported five children with hypsarrhythmia-like pattern on EEG. The age-specific hypsarrhythmia pattern is assumed to be the result of exaggerated cortical excitability reminiscent of the brain maturation period from 3 months to 2 years.

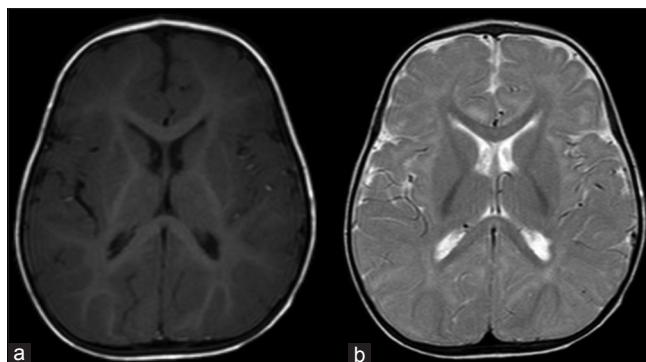
In addition, recognition of this hypsarrhythmia pattern in AS helps in appropriate management. Misdiagnosis as West syndrome and treatment with vigabatrin may worsen the symptoms, especially seizures.<sup>[9]</sup> The distinguishing features in AS are the absence of changes in EEG from awake to sleeping state and a less chaotic background.<sup>[10]</sup> A new-onset tremulousness and clinicoelectrographic discordance with hypsarrhythmia pattern in the absence of clinically evident epileptic spasms, are additional clues to AS in very young children. Furthermore, it is imperative to rule out AS in undiagnosed children with refractory epilepsy, maladaptive behavioral phenotype, and severe intellectual disability.

## CONCLUSION

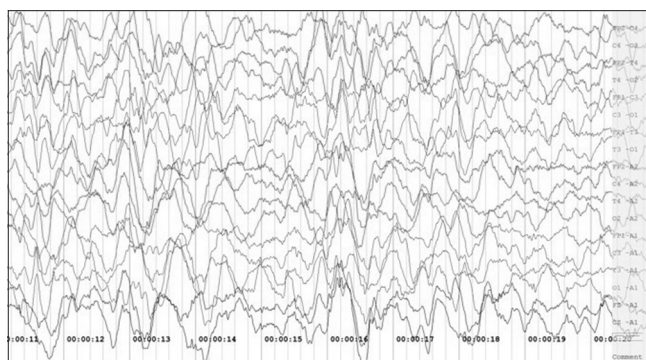
Pseudo-hypsarrhythmia pattern is poorly recognized yet, a clue to the early diagnosis of AS in infants and toddlers. Serial electrographic recordings may show the complete constellation of EEG changes suggestive of AS over time. Early detection in very young children before complete phenotype expression provides the opportunity for early intervention, genetic diagnosis, and prenatal counseling.

## Declaration of patient consent

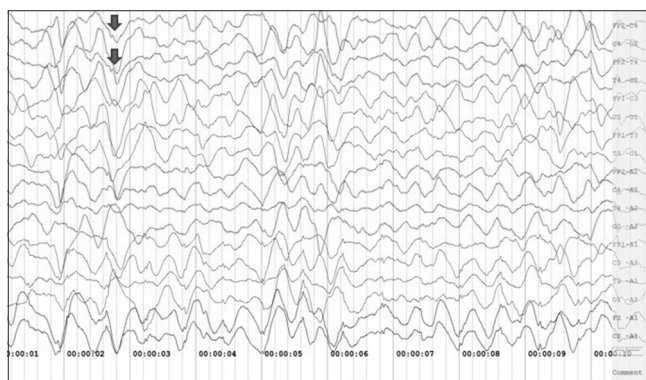
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.



**Figure 1:** T1 (a) and T2 (b) axial magnetic resonance imaging of the brain at eight months of age was unremarkable



**Figure 2:** Electroencephalography recording showing abnormal pattern during sleep with runs of high amplitude generalized irregular delta waves with multifocal epileptiform discharges suggestive of pseudo-hypsarrhythmia with a chaotic background. Pediatric montage; Sensitivity: 10 microvolt/mm; Sweep; 30 mm/s; Low filter: 1 Hz; High filter: 70 Hz



**Figure 3:** Electroencephalography recording during sleep showing rhythmic delta activity more pronounced in the frontal region with superimposed notched appearance on the descending phase of the slow wave. Pediatric montage; Sensitivity: 10 microvolt/mm; Sweep; 30 mm/s; Low filter: 1 Hz; High filter: 70 Hz

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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## REFERENCES

1. Bird LM. Angelman syndrome: Review of clinical and molecular aspects. *Appl Clin Genet* 2014;7:93-104.
2. Buiting K, Williams C, Horsthemke B. Angelman syndrome – Insights into a rare neurogenetic disorder. *Nat Rev Neurol* 2016;12:584-93.
3. Leyser M, Penna PS, de Almeida AC, Vasconcelos MM, Nascimento OJ. Revisiting epilepsy and the electroencephalogram patterns in Angelman syndrome. *Neurol Sci* 2014;35:701-5.
4. Vendrame M, Loddenkemper T, Zarowski M, Gregas M, Shuhaiber H, Sarco DP, *et al.* Analysis of EEG patterns and genotypes in patients with Angelman syndrome. *Epilepsy Behav* 2012;23:261-5.
5. Dan B. Angelman syndrome: Current understanding and research prospects. *Epilepsia* 2009;50:2331-9.
6. Boyd SG, Harden A, Patton MA. The EEG in early diagnosis of the Angelman (happy puppet) syndrome. *Eur J Pediatr* 1988;147:508-13.
7. Valente KD, Andrade JQ, Grossmann RM, Kok F, Fridman C, Koiffmann CP, *et al.* Angelman syndrome: Difficulties in EEG pattern recognition and possible misinterpretations. *Epilepsia* 2003;44:1051-63.
8. Mayo O, Nelson MM, Townsend HR. Three more 'happy puppets'. *Dev Med Child Neurol* 1973;15:63-74.
9. Darteyre S, Mazzola L, Convers P, Lebrun M, Ville D. Angelman syndrome and pseudo-hypsarrhythmia: A diagnostic pitfall. *Epileptic Disord* 2011;13:331-5.
10. Laan LA, Vein AA. Angelman syndrome: Is there a characteristic EEG? *Brain Dev* 2005;27:80-7.

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