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Extreme Sleep Spindles in Children with Autism Spectrum Disorder and Related Disorders—A Case Series

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Abstract

Extreme sleep spindles have fast activity and high amplitude, unlike normal sleep spindles. We report a case series of six children with autism and related disorders who had extreme spindles as noted on the sleep electroencephalogram recording at our center. We examine the types of extreme spindles, describe the clinical profiles of the 6 children, and discuss similar clinical and neurophysiological conditions.

Keywords

- autism
- EEG
- extreme spindles
- neurodevelopmental disorders
- sleep spindles

Introduction

Sleep spindles are powerful synchronous bursts of activity in stage 2 of sleep, between 10 and 14 Hz frequency, with the maximum amplitude in the central leads. Sleep spindles are generated from the thalamocortical relay cells in the thalamic reticular nucleus and are observed as the surface correlates of these neuronal oscillations in the thalamus.[1,2]

Unlike normal sleep spindles, occasionally there can be an activity that is of high amplitude (up to 200 microvolts) and is more widely distributed. Such sleep spindles of high amplitude and wide distribution are called "extreme spindles."[3,4] Extreme spindles are characterized by their diffuse expression (14 to 16 Hz), continuous, fast waves with high amplitude (200–500 microvolts), and a sharp morphology, during light sleep[3–5] and sometimes persistence in the awake state. These can last up to 20 seconds.[6] It has been speculated that extreme spindles are caused by the disruption of regulatory mechanisms, including GABAergic inhibitory circuits,[6] but the exact mechanism responsible for extreme spindles is unknown. It has no association with epilepsy.

Extreme spindles are known to be associated with neurodevelopmental disorders, predominantly intellectual disability (ID), Costello syndrome (ID, developmental delay, unusually flexible joints, and facial dysmorphisms), malformations of cortical development, and children with autism spectrum disorder (ASD).[5] It is also described in neuroinfections,[7] infantile neuroaxonal dystrophy, Menke's kinky hair syndrome, congenital muscular dystrophy, and anti-N-methyl-D-aspartate receptor encephalitis.[8]

In children with ASD without epilepsy, electroencephalogram (EEG) is not routinely performed in clinical practice. Even if done, it is difficult to perform a sleep EEG on these children. Hence, this interesting finding of extreme spindles is not commonly encountered. In our center for children with

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Table 1 Clinical profiles of children with ASD and extreme spindles

Case no.	Age/sex	Primary diagnosis	Clinical presentation	History of seizures	Medication	EEG finding
1	4 years, 3 months/male	GDD	GDD with dysmorphic features, hyperactivity, and significant speech delay	No	None	Moderate cerebral dysfunction (suggested by background theta activity) and bifrontal epileptiform discharges with extreme sleep spindles
2	9 years, 4 months/male	ASD	ADHD and behavioral issues, with a diagnosis of ASD with significant speech delay	No	Methylphenidate 10 mg/day	Otherwise, normal study with extreme sleep spindles
3	4 years, 3 months/male	ASD	Significant speech and language delay diagnosed with ASD and obesity	No	None	Otherwise, normal study with extreme sleep spindles
4	3 years, 2 months/male	ASD	Developmental regression since 1 year, 6 months of age, significant language and cognitive delay, with a diagnosis of ASD. Sleep disturbances (predominantly insomnia) were reported since onset of regression	No	Ayurvedic medication	Otherwise, normal study with extreme sleep spindles
5	2 years, 4 months/female	ASD	Developmental regression, significant language and cognitive delay, autism features, hyperactivity, and sleep disturbances (predominantly insomnia) of 6 months duration	No	None	Background asymmetry with extreme sleep spindles
6	7 years, 5 months/male	ASD	Poor response to therapy, significant speech, and language delay	No	None	Otherwise, normal study with extreme sleep spindles

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; GDD, global developmental delay.

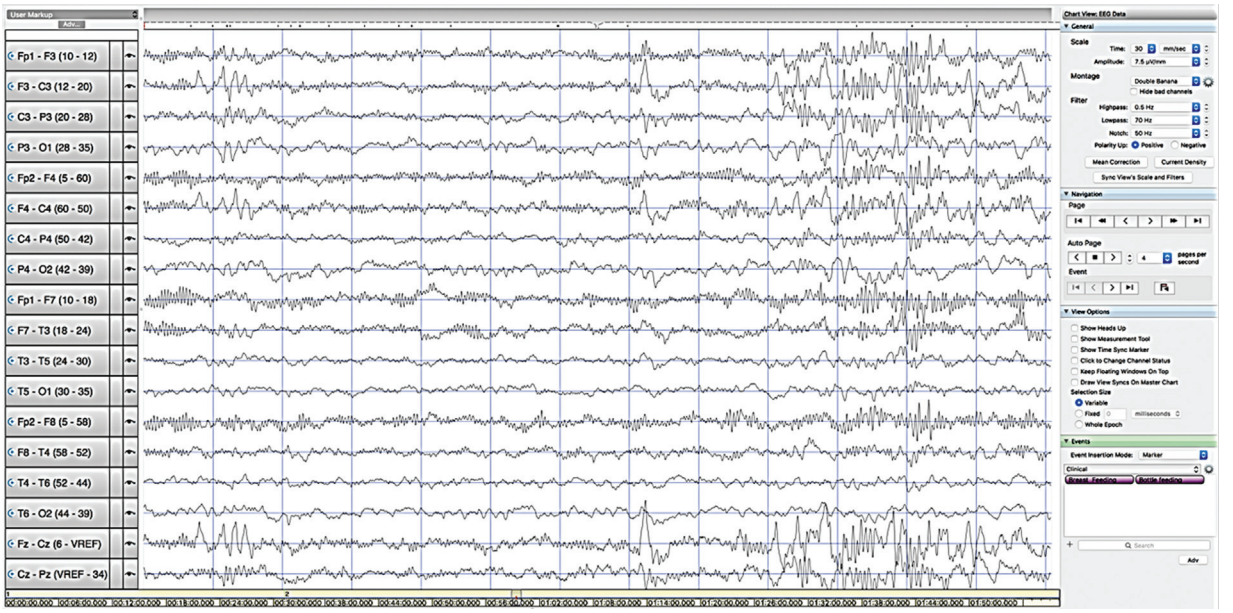

Fig. 1 Type 2b extreme spindles with lower amplitude.

ASD, we follow a standard research protocol of awake and sleep EEG, preferably spontaneous sleep record, lasting from 1 to 4 hours. With this protocol, we have observed this phenomenon in children with ASD and related disorders. In this article, we present a case series of children with ASD/related disorders with extreme spindles and explore the possible mechanisms.

Case Series

Two-hundred eighty-nine children underwent EEG at our center of which there were 163 children with ASD and 126 children with other neurological/neurodevelopmental disorders. Of these, 6 children had extreme spindles. Their ages ranged from 2 years, 4 months to 9 years, 4 months. Five were male children and one was a female child. Five had a primary diagnosis of ASD and one had global developmental delay. Two children had a history of developmental regression. All six children had cognitive delay. Two children had sleep difficulties, predominantly insomnia. None of the six children had a history of seizures (►**Table 1**).

On examination of our case series, three children had type 3 extreme spindles, two had type 6, and one had type 2b with a lower amplitude as per the classification by Gibbs and Gibbs (►**Figs. 1–6** ►**Table 2**).[3] ►**Figs. 1–6** are displayed in bipolar, longitudinal montage, at a sensitivity of 7.5 μV/mm and filter settings of 0.5-70 Hz. Each image is from each patient in the case series (►**Table 1**)

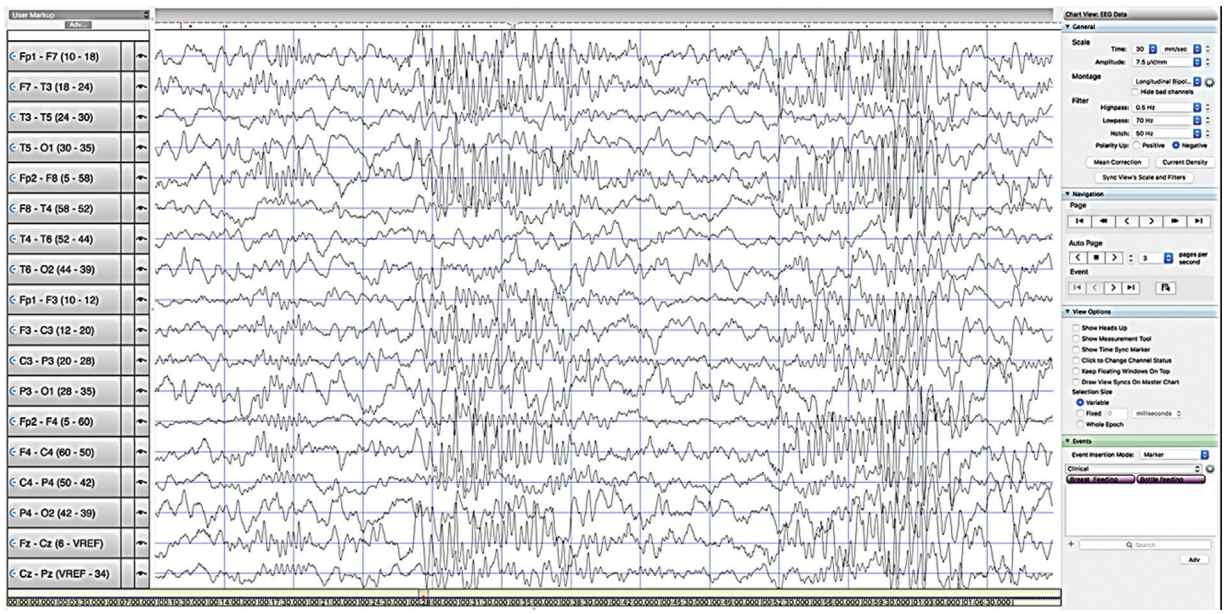

Fig. 2 Type 3 extreme spindles.

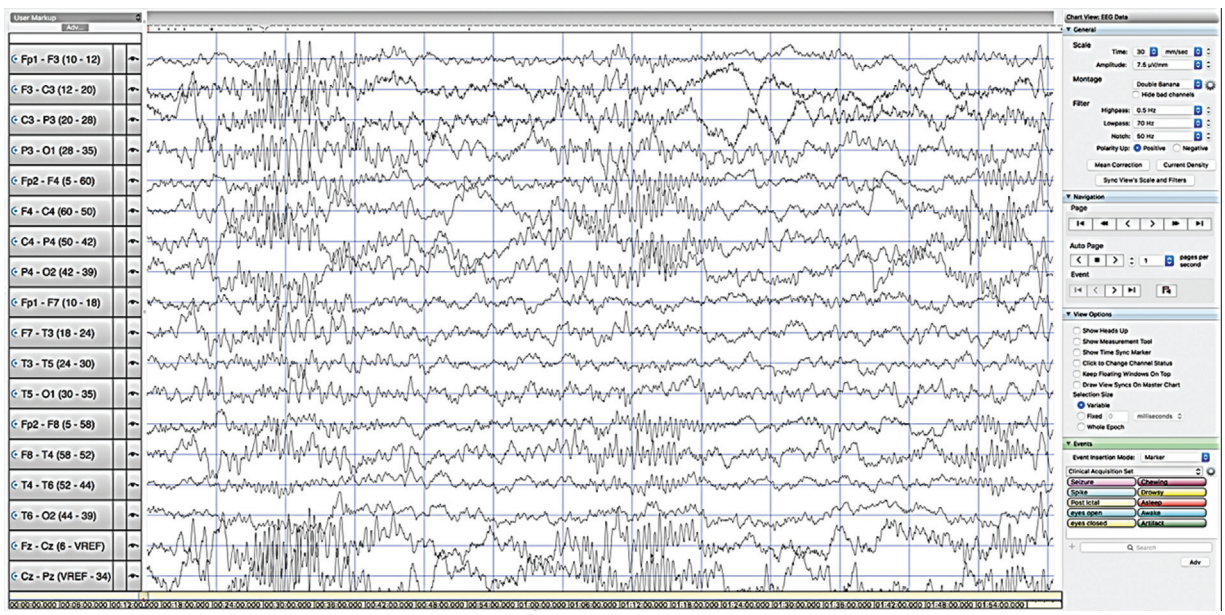

Fig. 3 Type 3 extreme spindles.

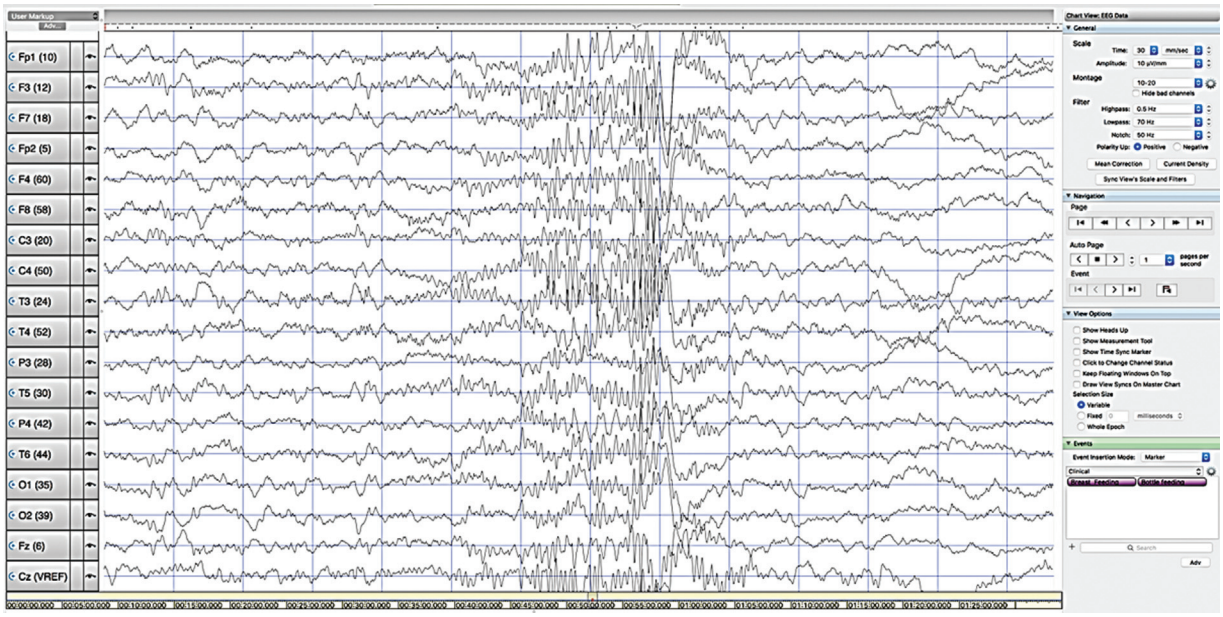

Fig. 4 Type 3 extreme spindles.

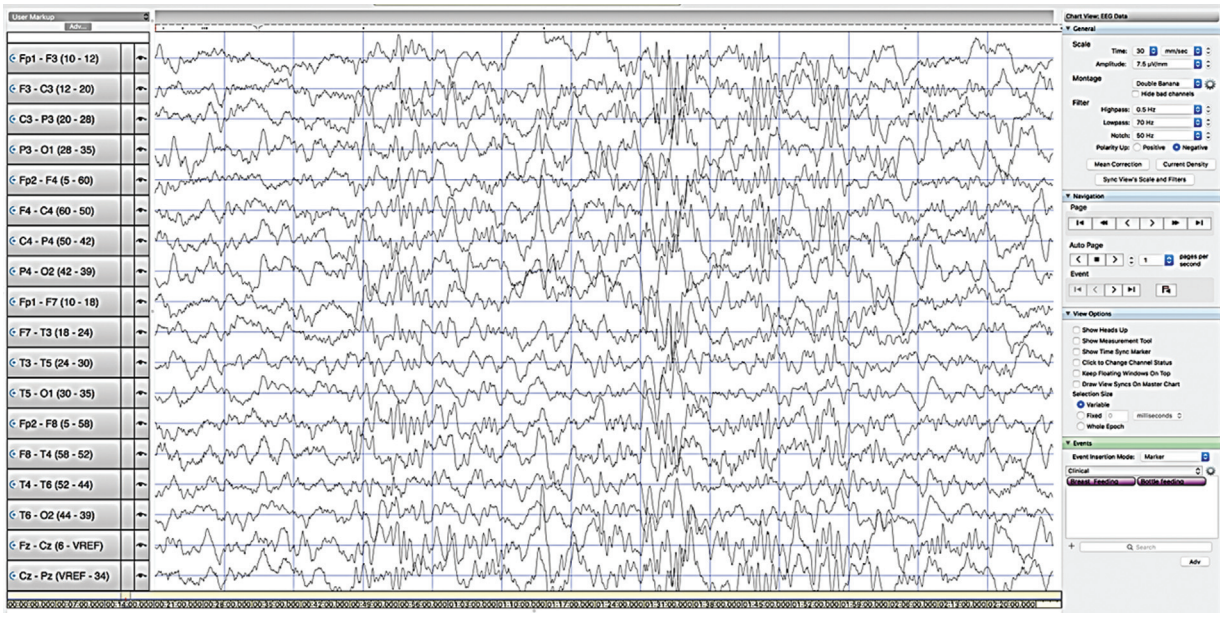

Fig. 5 Type 6 extreme spindles.

demonstrating the type of extreme spindle as per Gibbs and Gibbs.[3] In our small series, type 3 spindles, which are of high amplitude and spiky appearance resembling epileptiform discharges, were the most common type and were seen in three children. Most of these spindles were seen in stages 2 of nonrapid eye movement sleep. All children with type 3 and 6 had spindles with an amplitude ranging between 200 and 350 microvolts. One child also had bifrontal epileptiform discharges in the absence of clinical seizures. Another child had asymmetric background activity. In the remaining four children, extreme spindle activity was the only abnormality in the EEG.

Discussion

This is probably the first of such series reported from India on the ASD population. In our study sample, of the six children with extreme spindles, four of them did not have any other abnormalities on EEG. One had background asymmetry and another had background slowing with epileptiform discharges. Five of six children were males and three of six children had hyperactivity as comorbidity. One child was on medication. As described by Gibbs and Gibbs, we found three different types of extreme spindles in our case series (types 2b, 3, and 6). We did not find extreme spindles in any of the

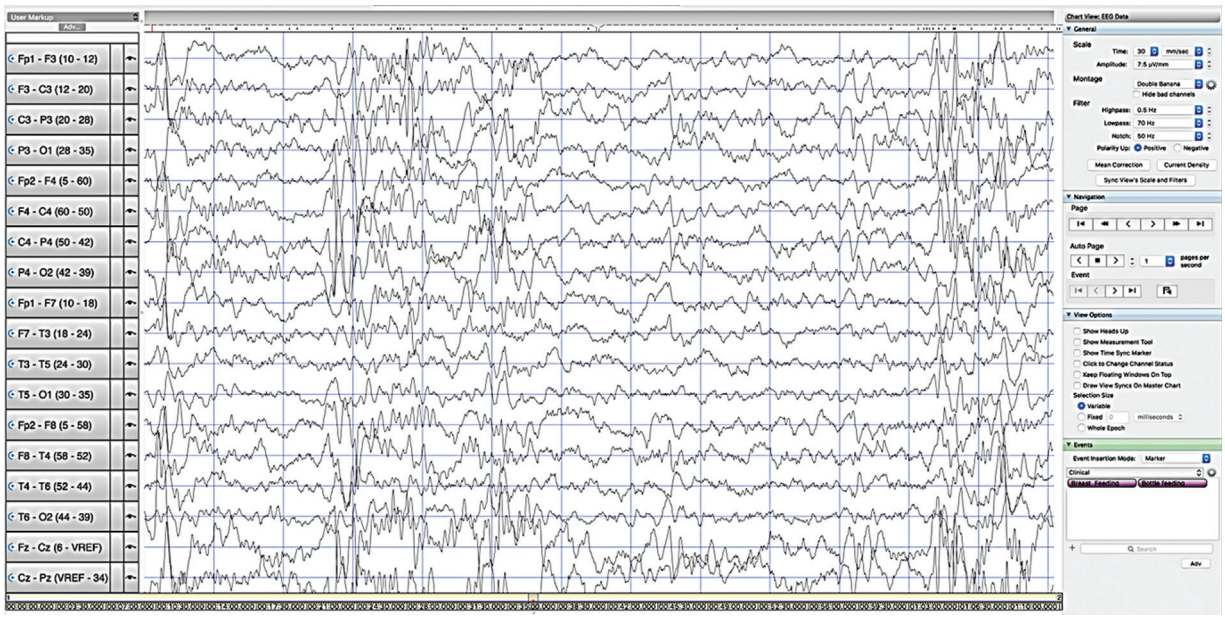

Fig. 6 Type 6 extreme spindles.

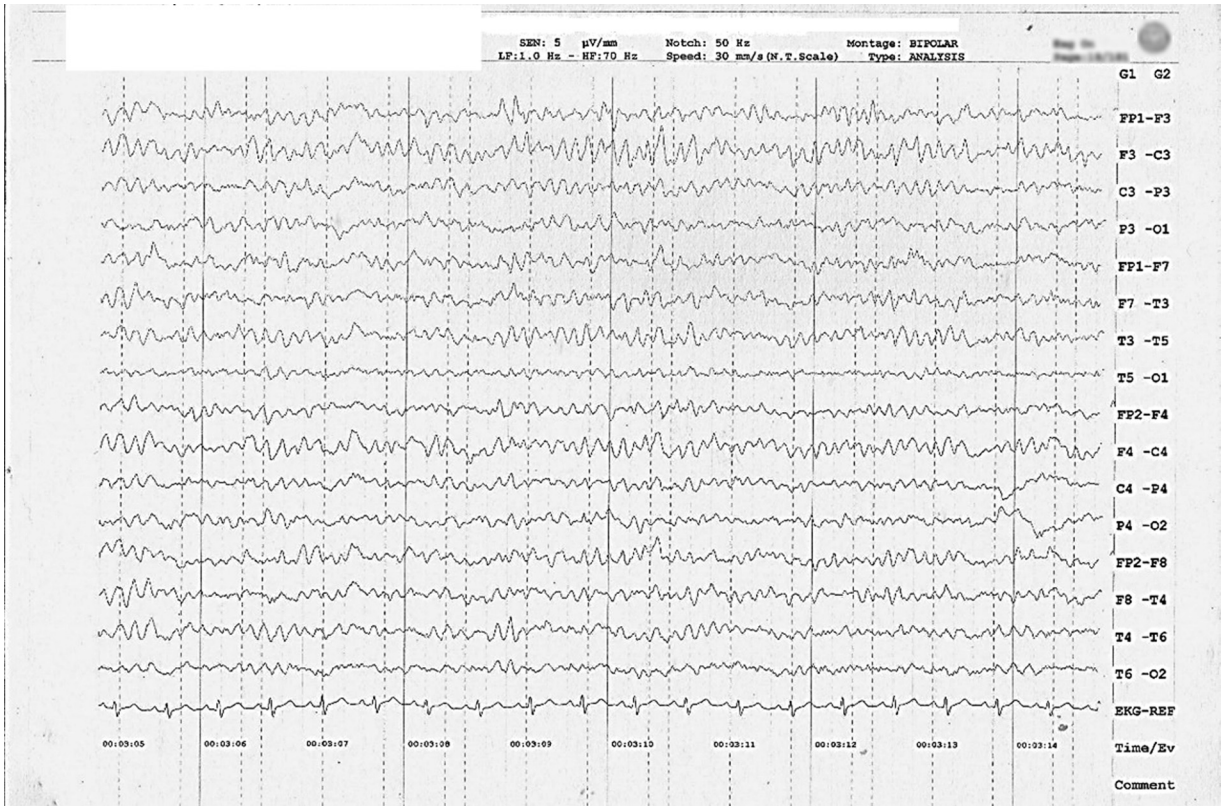

Fig. 7 Example of alpha coma.

other children who underwent EEG at our center with a primary diagnosis other than ASD including cerebral palsy, attention deficit hyperactivity disorder, learning disability, epilepsy, psychosis, tics, or pseudoseizures.

The significance of the presence of sleep spindles and their clinical implications in children with ASD are not clearly known. Extreme spindles have been previously reported in children with ASD, mental retardation, and other neurodevelopmental disorders. Children with IDs are known to be associated with a wide variety of genetic and developmental alterations. The presence of significant cognitive delay resulting in comorbid ID, especially in children with regression and severe forms of ASD with multiple comorbidities, could be a contributory factor to

the presence of extreme spindles.[5,9] Some studies have also mentioned the presence of a lower density of sleep spindles and fewer spindles over the central and prefrontal areas.[1] Too few spindles or extreme spindles are also both associated with ID.[1,5] In this case series, all children with ASD had ID as comorbidity. This could be one of the factors that are contributing to the occurrence of extreme spindles rather than fewer spindles or spindles with lower density.

Extreme spindles must also be differentiated from spindle coma, beta coma, and alpha coma (►**Figs. 7**, **8**). Spindle coma is different from extreme spindles with characteristics of 11 to 14 Hz spindle discharges in comatose patients where the background is predominantly theta or delta. EEG patterns have frequent bursts of sleep-like activity, mostly due to the presence of thalamocortical circuits and raphe nuclei activity, but the absence of activity in the reticular activating pathways in the midbrain.[10] Alpha coma, on the other hand, is an EEG pattern seen in cases of profound coma as a result of trauma, encephalitis, drug overdose, or hypoxic-ischemic encephalopathy that is seen as a diffuse band of alpha frequency across all the leads.[11] Extreme spindles must also be differentiated from beta coma.[12] This occurs typically due to benzodiazepine toxicity or barbiturate use and is seen as discharges of 13 to 30 Hz with low amplitude beta activity that overrides normal activity throughout the recording (►**Fig. 8**).

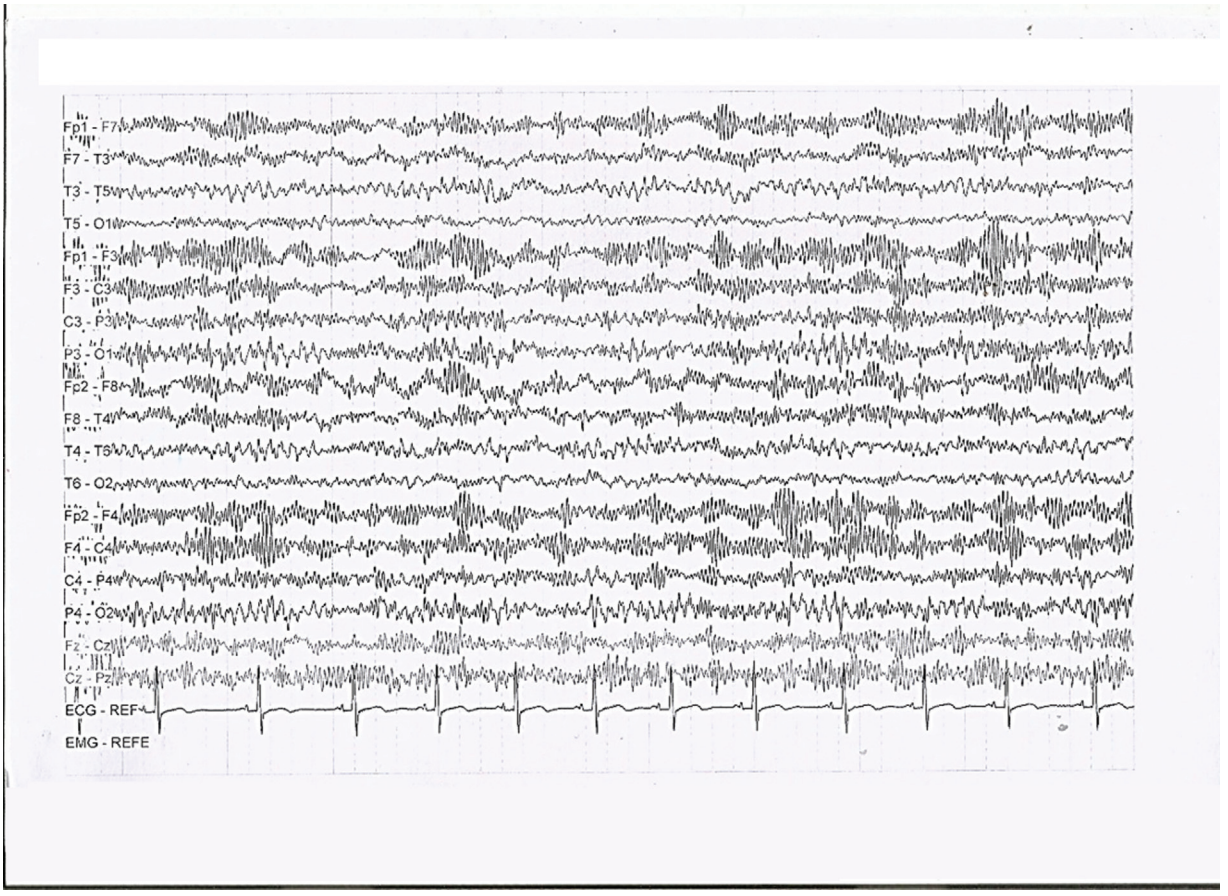

Fig. 8 Example of beta coma.

Table 2 Types of extreme spindles as described by Gibbs and Gibbs[3]

Type	Description
1	12–14 Hz, almost continuous, high voltage spindles in sleep
2	Similar to type 1 but particularly fast activity in drowsiness and sleep (further divided as 2a and 2b)
3	"Spiky" high voltage spindles that resemble epileptiform discharges
4	Spindles of high voltage that are fast in early sleep stages but slow down to 6Hz in deeper stages (further divided as 4a, 4b, and 4c)
5	Very frequent, almost continuous slow spindles of 5–7 Hz frequency
6	Mixture of two or more types

In conclusion, children with ASD can have multiple overlapping neurodevelopmental comorbidities, sleep disorders, and epilepsy co-occurring with the core symptoms. The shared biological pathways may contribute to the occurrence of these extreme spindles. There is a need to further understand these findings from clinical, genetic, and neurological perspectives to inform clinical care, and interventions.

Note

This series is part of a larger ongoing study with ethics approval (IEC.No.379/2021).

Conflict of Interest

None declared.

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