

# Epilepsy and EEG Findings in Children with Autism Spectrum Disorders

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## Abstract

**Background:** Epilepsy is strongly associated with Autism Spectrum Disorders (ASD). This high rate of epilepsy suggests that ASD and epilepsy might share a common pathophysiological basis.

**Objective:** To study the characteristics of EEG findings and epilepsy in autistic spectrum disorders (ASD) and the associated neuropsychological symptoms.

**Methods:** Thirty children with ASD, aged from 3 to 11 years old, were included in the study. EEG recordings were obtained for each child. All patients were evaluated with respect to clinical and familial characteristics and with the Childhood Autism Rating Scale (CARS).

**Results:** The frequency of epileptiform EEG abnormalities in children with ASD was 40%, and the frequency of epilepsy was 30%. EEG abnormalities were associated with a diagnosis of epilepsy in 13.3%. Seizures and EEG changes were frequent among children with severe autism. Aggressive behaviours, hyperactivity and delayed developmental history were more frequent among patients with seizures. Sleep disturbance and hyperactivity were more common among participants with severe autism. On the other hand, aggressive behaviour and developmental delay were more common among patients with mild to moderate autism.

**Conclusion:** Autism is one of the risk factors for epilepsy. Epilepsy occurs in one-third of patients with ASD. EEG abnormalities occur in 40% of patients with ASD. Epilepsy may be considered as one of the aggravating factors for behavioural/emotional outcomes for individuals with autism. Treatment of EEG changes might have a positive effect on the symptomatic improvement of children with ASD and EEGs changes.

**Keywords:** Epilepsy; EEG; Autism spectrum disorders

## Introduction

Autism is a neurodevelopmental disorder of social reciprocity and communication, with a specific behavioural profile consisting of repetitive behaviours and restricted interests. It should be noted that the social communication deficits and behavioural profile cannot be better explained by intellectual disability, which is an especially common comorbidity in those with both autism and epilepsy [1].

Kim et al. stated that frequency of epilepsy in autism ranges from 4% to 42% [2]. A significant majority of patients with ASD have interictal epileptiform EEG abnormalities (IIEAs) on routine EEG studies, without seizures [3]. The incidence of IIEAs in autistic individuals was found to be between 6% and 74% [4].

Previous studies have reported age, mental status and neurological findings as risk factors for epilepsy in ASD. There is a bimodal age distribution of seizures in autism: one peak occurs before 5 years of age and the other in adolescence after age 10. Individuals with ASD who have profound mental retardation and/or cerebral palsy are at high risk for epilepsy [2].

## Patients and Methods

This study was cross-sectional study that conducted in the Neuro-Pediatric clinic in Fayoum University Hospital. It included thirty patients diagnosed with ASD according to Diagnostic and Statistical manual of Mental disorders of the American Psychiatric Association 5th edition (DSM-5) [1]. Patients with hearing impairment, cerebral palsy, dysmorphic features and definite neurological disorders e.g. patients with tuberous sclerosis, patients with phenylketonuria were excluded.

Patients were assessed for degree of severity of autism by using Childhood Autistic Rating Scale (CARS). This group of children was collected during the time period from April 2015 to March 2016.

The patients were referred to the Neuro-Pediatric outpatient clinic to be interviewed. Sheets were fulfilled from all the participants with the help of their caregivers. Childhood Autistic Rating Scale (CARS) was applied to each patient to assess the the severity of the disorder [5].

Details regarding history of seizures, their types, frequency, age of onset and therapeutic measures were reported, History of neuropsychological symptoms as sleep disturbance, hyperactivity, aggressiveness was taken. EEG was done for each patient. Brain MRI was done for indicated cases (mild delay of motor development).

Informed oral consents were taken from all the caregivers of the participants included in the study.

## Statistical Analysis of Data

The collected data was organized, tabulated and statistically analyzed using SPSS software statistical computer package version 18 (SPSS Inc., USA). For quantitative data, the mean, standard deviation, median and range were calculated. Mann-Whitney U test was used as test of significance. For qualitative data the number and percent distribution was calculated, Chi squared test or Fischer exact test when appropriate was carried out as a test of significance. For interpretation of results of tests of significance, significance was adopted at P<0.05.

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## Results

study included thirty patients (42 males and 18 females) diagnosed with ASD. The age of participating children ranged between 3 and 11 years old with a median age was 3.5 years. The age of mothers of participating children ranged between 16 and 36 years old with a median age 26 years. 20% of participant had positive consanguinity. Hypotonia was observed in some patients with normal or hyporeflexia of both upper and lower limbs. However, these children had normal motor developmental milestones. Other data regarding medical history, nutrition, family history of psychiatric, autoimmune or neurological diseases and some clinical findings of study participants were included in Table 1.

Regarding neuropsychological history among study participants: 76.7% had aggressive behaviours, 76.7% had hyperactivity, 76.7% had delayed mental development and 36.7% had sleep disturbances (Figure 1).

Regarding frequency and characteristics of seizures among study participants: 30.0% had Seizures (55.6% had generalized tonic clonic seizures, 22.2% Myoclonic seizures, 11.1% Febrile convulsion, and 11.1% had Complex focal convulsion). Regarding EEG findings among study participants: 41.7% had slow waves, 41.7% had Focal epileptogenic activity (Figure 2), 8.3% had generalized epileptogenic activity and 8.3% had mixed; slow waves with focal epileptogenic activity (Table 2). Only 8/24 of patients who had EEG changes, had history of seizures. Three of them were classified as severe autism.

Regarding distribution of study participants as regard grade of autism as diagnosed by CARS, Figure 3 showed that: 30.0% had mild to moderate autism while 70.0% had severe autism.

As regard the relation between seizures and the mean of CARS and neuropsychological problems, Table 3 showed that Children with seizures had higher level of CARS than those without seizures (mean  $\pm$  SD: 40.6  $\pm$  5.1 vs. 39.2  $\pm$  5.2) but the difference was not statistically significant,  $p=0.510$ .

Although sleep disturbances were more common among patients without seizures (81.0% vs. 66.7%), it was not statistically significant,  $p=0.640$ . Conversely, Aggressive behavior, hyperactivity and delayed developmental history were more frequent among patients with seizures (77.8% vs. 76.2%), for all of them, also, it was not statistically significant,  $p=0.141$  for aggressive behavior and 1.000 for hyperactivity and developmental history.

As regard the relation between EEG changes and the mean of CARS and neuropsychological problems, Table 4 showed that children with EEG changes had higher level of CARS than those without EEG changes (mean  $\pm$  SD: 41.1  $\pm$  5.1 vs. 38.6  $\pm$  4.9) but the difference was not statistically significant,  $P=0.197$ .

Although sleep disturbance and aggressive behavior were more common among patients with EEG changes (50.0% vs. 27.8% and 83.3% vs. 72.2%, respectively), it was not statistically significant,  $P=0.266$  and 0.669, respectively. Conversely, hyperactivity and developmental history were more frequent among patients without EEG changes (77.8% vs. 75.0%), for both, it was statistically insignificant,  $P=1.000$ .

Regarding the relation between grades of autism and seizures, Figure 4 showed that percentage of participants with seizures was higher among children with severe autism than children with mild to moderate autism (33.3% vs. 22.2%). However,  $p$ -value was insignificant ( $p=0.681$ ).

Regarding the relation between grades of autism and EEG changes, (Figure 5) showed that percentage of participants with EEG changes

was higher among children with severe autism than children with mild to moderate autism (42.9% vs. 33.3%).  $P$ -value was insignificant ( $p=0.704$ ).

As regard the relation between grades of autism and neuropsychological symptoms Table 5, showed that sleep disturbance and hyperactivity were more common among participants with severe autism than participants with mild to moderate autism (47.6% vs. 11.1%, and 81.0% vs. 66.7%, respectively).  $P$ -value was insignificant ( $p=0.1$  and 0.640, respectively). On the other hand, aggressive behaviour and developmental delay were more common among patients with mild to moderate autism than severe autism (88.9% vs. 71.4% and 88.9% vs. 71.4%, respectively).  $P$ -value was insignificant ( $p=0.393$  for both).

## Discussion

Autism spectrum disorders (ASD) are neurological and developmental disorders characterized by an impairment of social relatedness,

Variable	Median	Range
Age (years)	3.5	3-11
Maternal age (years)	26.0	16-36
	No(N=60)	%
<b>Sex:</b>		
Male	42	70.0%
Female	18	30.0%
<b>Consanguinity:</b>		
+ve	12	20.0%
-ve	48	80.0%
<b>Medical conditions</b>		
<b>+ve</b>		
• Surgical operation for hydrocele+lipoma in the neck	2	3.3%
• VSD+Neonatal sepsis	2	3.3%
• Jaundice with exchange transfusion	2	3.3%
• Ear infection	4	6.6%
• FUO	2	3.3%
• Anemia	4	6.6%
	16	26.7%
<b>-ve</b>	44	73.3%
<b>Nutrition</b>		
<b>Breast feeding</b>	40	66.7%
<b>Artificial formula</b>	10	16.7%
<b>Mixed</b>	10	16.7%
<b>Family history of psychiatric, autoimmune or neurological diseases</b>		
<b>+ve</b>		
• Autism	2	3.3%
• Maternal arthritis	4	6.7%
• Epilepsy	4	6.7%
• Asthma	2	3.3%
• Vitiligo	2	3.3%
	14	23.3%
<b>-ve</b>	46	76.7%
<b>Clinical findings of study participants</b>		
<b>Macrocephaly (HC&lt;97<sup>th</sup> percentile):</b>		
Present	14	23.3%
Absent	46	76.7%
<b>Hypotonia:</b>		
Present	20	33.3%
Absent	40	66.7%

Table 1: Distribution of study participants as regard medical history.

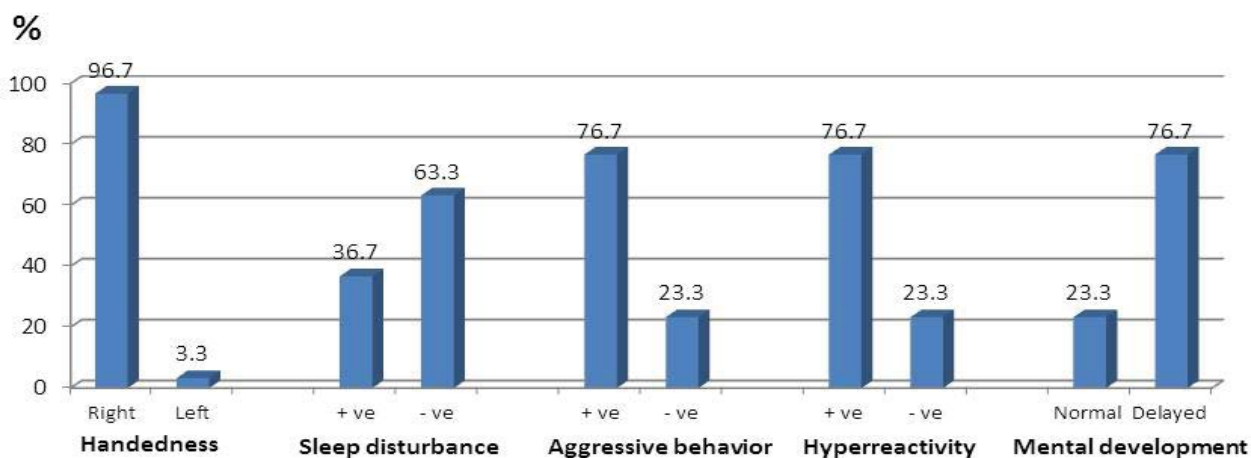


Figure 1: Distribution of study group regarding neuropsychological history.



Figure 2: EEG of a 6 year old girl with severe autism, showing picture of encephalopathy with left frontocentral epileptogenic discharge.

communication skills, restriction of interests and stereotyped behaviours [6]. ASD is believed to be related to central nervous system (CNS) dysfunction, Epilepsy is strongly associated with ASD, with a wide range of estimates from 5 to 46%. This high rate of epilepsy suggests that ASD and epilepsy might share a common pathophysiological basis. However, there is no consensus regarding the neuropathophysiology of ASD [7].

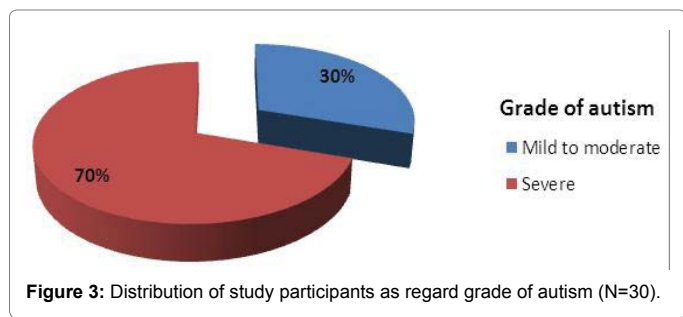
According to the current study, 30% of ASD patients have epilepsy and 40% showed definite epileptiform paroxysmal discharges or a slow and disorganized background rhythm. These patients largely showed associated clinical problems, such as sleep disturbances, behavioural problems and a regression of language. According to Tuchman and Rapin, there is a bimodal age distribution of seizure in ASD [8]. The first peak is in infancy before 5 years of age, and the second peak is in

adolescence, after 10 years of age [9]. In the current study the ages of cases who have epilepsy range from 3 to 11 years with higher percentage among the cases whose ages are below 5 years (7/9=77.8%).

In this study, only 20% of patients have history of positive consanguinity. This didn't reflect any statistical significance indicating that positive consanguinity is not considered as a risk factor for autism. This agreed with another Egyptian study done in Ain Shams University which also showed that the control group had higher percentages of positive consanguinity (21.5%) than the patients group (13%) [10]. However, this was not consistent with a study done in Saudi- Arabia which found that 1/3 of a group of children with autism had a history of positive consanguinity. But still, it is important to notice that consanguineous marriage in Saudi Arabia reaches up to 80% of marriages especially in rural communities [11].

Variable	Number	Percentage
<b>Seizures:</b>		
Present	18	30.0%
Absent	42	70.0%
<b>Types of seizures (N=9):</b>		
Febrile convulsion	2	11.1%
Generalized tonic clonic	10	55.6%
Myoclonic	4	22.2%
Complex focal convulsion	2	11.1%
<b>EEG changes:</b>		
Present	24	40.0%
Absent	36	60.0%
<b>Characteristics of EEG changes (N=12):</b>		
Slow waves	10	41.7%
<b>Epileptogenic activity:</b>		
Generalized	2	8.3%
Focal	10	41.7%
Mixed; slow waves with focal epileptogenic activity	2	8.3%

**Table 2:** Frequency, characteristics of seizures and EEG findings among study participants (N=60).



**Figure 3:** Distribution of study participants as regard grade of autism (N=30).

	Patients with seizures (N=18)		Patients without seizures (N=42)		p-value
	No	%	No	%	
<b>CARS</b>					
Mean ± SD	40.6 ± 5.1		39.2 ± 5.2		0.510
Sleep disturbance					
Positive	12	66.7%	34	81.0%	0.640
Negative	6	33.3%	8	19.0%	
Aggressive behaviour					
Positive	14	77.8%	32	76.2%	0.141
Negative	4	22.2%	10	23.8%	
Hyperactivity					
Positive	14	77.8%	32	76.2%	1.000
Negative	4	22.2%	10	23.8%	
Developmental history					
Delayed	14	77.8%	32	76.2%	1.000
Normal	4	22.2%	10	23.8%	

**Table 3:** Relation between seizures and the mean of CARS and neuropsychological problems.

Autism spectrum disorder is believed to be a disorder with high heritability, and many genetic studies have focused on multiplex families (i.e., those with more than one family member affected with ASD). An investigation of epilepsy risk in a large study of multiplex families with ASD showed an epilepsy rate of 12.8% in the children with ASD and also 2.3% in the siblings without ASD, a rate more than double that of the general population. This suggests that there is a genetic burden not only for ASD and also for epilepsy in the families with more than one member affected with ASD [12].

Similarly, a longitudinal study of the incidence of epilepsy in ASD reported that the presence of epilepsy was independently associated

with a broader autism phenotype in relatives (i.e., sub threshold autistic traits) [13]. Studies also show that a family history of epilepsy is associated with an increased risk of epilepsy in those with ASD [4,14,15].

In the current study, family history of psychiatric, neurological or autoimmune diseases is present in 20% of cases in the form of Autism, epilepsy, maternal arthritis, asthma and vitiligo.

Different types of seizures can be associated with autism [7], which is consistent with the current results, where five cases had history of generalized tonic clonic seizures, two cases had history of myoclonic seizures, one case had history of complex focal seizures and another case had history of febrile seizures.

Some studies provide a breakdown of epilepsy prevalence among the types of ASD according to severity. Most studies report that epilepsy is more frequent in severe autism compared to mild to moderate autism. A previous study reported an epilepsy rate of 9.8% of patients with severe autism, and only 3.1% of patients with mild to moderate autism. Some of this may be due to the association of epilepsy with intellectual disability (ID) since the rates of ID were higher in the groups with severe autism than in the group with mild to moderate autism (28.8% and only 1.3%, respectively) [15], which agrees with the current study as it shows that, percentage of children with seizures was higher among children with severe autism than in mild to moderate autism (33.3% vs. 22.2%).

The EEG results are variable and 12/30 patients (40%) showed EEG changes. These EEG change might be considered a biomarker of a cortical dysfunction in this population. There are no specific epileptiform EEG patterns known in ASD patients yet. These EEG changes can show the following: slowing, asymmetry, spikes, sharp and slow waves, generalized sharp and slow waves or generalized polyspikes in diffuse or generalized, multifocal or focal discharges, unilateral or bilateral and localized to many different brain areas [16]. In our study, percentage of children with EEG changes was higher among children with severe autism than mild to moderate autism (42.9% vs. 33.3%), but there was no statistical significance.

Although there was no statistical significance, there was slightly higher association of neuropsychological problems in patients with epilepsy and patients with EEG changes. Whether we should treat these epileptiform EEG abnormalities even if the patient does not

	Patients with EEG changes (N=24)		Patients without EEG changes (N=36)		p-value
	No	%	No	%	
<b>CARS</b>					
Mean ± SD	41.1 ± 5.1		38.6 ± 4.9		0.197
Sleep disturbance					
Positive	12	50.0%	10	27.8%	0.266
Negative	12	50.0%	26	72.2%	
Aggressive behavior					
Positive	20	83.3%	26	72.2%	0.669
Negative	4	16.7%	10	27.8%	
Hyperactivity					
Positive	18	75.0%	28	77.8%	1.000
Negative	6	25.0%	8	22.2%	
Developmental history					
Delayed	9	75.0%	14	77.8%	1.000
Normal	3	25.0%	4	22.2%	

**Table 4:** Relation between EEG changes and the mean of CARS and neuropsychological problems.



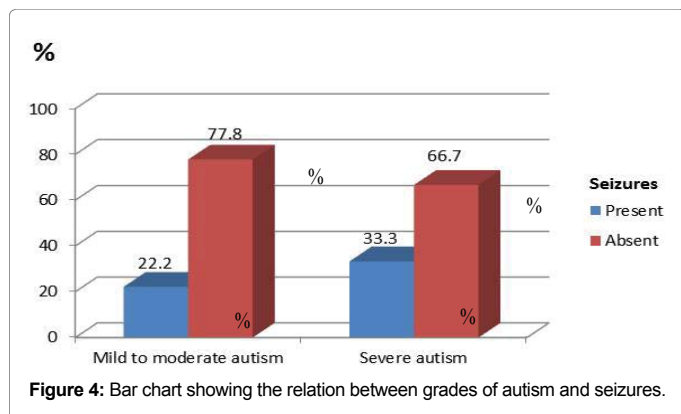


Figure 4: Bar chart showing the relation between grades of autism and seizures.

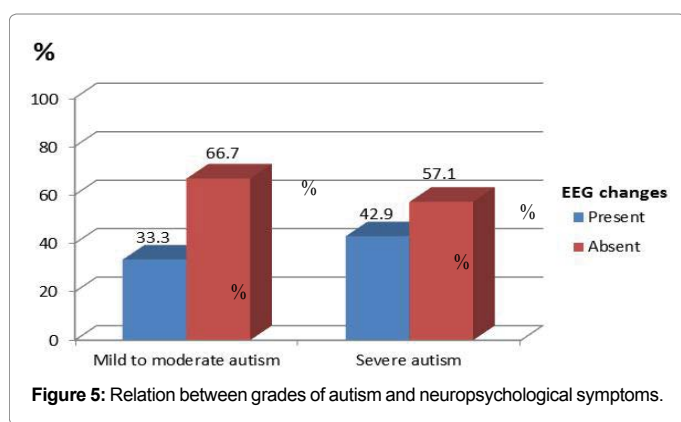


Figure 5: Relation between grades of autism and neuropsychological symptoms.

	Mild to moderate autism (N=18)		Severe autism (N=42)		p-value
	No	%	No	%	
Sleep disturbance					
Positive	2	11.1%	20	47.6%	0.100
Negative	16	88.9%	22	52.4%	
Aggressive behaviour					
Positive	16	88.9%	30	71.4%	0.393
Negative	2	11.1%	12	28.6%	
Hyperactivity					
Positive	12	66.7%	34	81.0%	0.640
Negative	6	33.3%	8	19.0%	
Developmental history					
Delayed	16	88.9%	30	71.4%	0.393
Normal	2	11.1%	12	28.6%	

Table 5: Relation between grades of autism and neuropsychological symptoms.

show clinical seizure is a controversial problem. Generally, interictal discharges are thought to interfere with normal neural processing.

ASD is frequently accompanied by co-morbid disorders and associated problems, one of which is sleep disruption [17]. Moreover, Cortesi et al. stated that about 40-80% of individuals with an ASD experience a sleep problem and the risk appears to be unrelated to the severity of cognitive impairment [18]. This agrees with our results as sleep disorders are present in 11/30=36.7% of cases. These disorders included bed time resistance, sleep onset delay, problem with sleep duration, night waking and day time sleepiness.

Children with ASD are at high risk for behavioural regulation difficulties, including aggression [19], irritability [20], inattention

and hyperactivity [21]. May et al., examined the associations between sleep and behaviour problems in children with ASD [22]. The results indicated significant correlations between sleep disturbance and both aggression and hyperactivity. Understanding, identifying, and treating sleep disorders in autism may impact favourably on associated conditions and daytime behaviour and therefore improve the quality of life in this population [17].

In our study, aggressive behaviour is present in 23/30=76.6% of cases, it is present at a percentage of 77.8% among those who have seizures, and 83.3% in cases with EEG changes. Hyperactivity is present in 23/30=76.6% of cases, it is present at a percentage of 77.8% among those who have seizures and 75% in cases with EEG changes.

Our study showed that the developmental regression was more frequent among autistic patients with seizures and EEG changes than others. However, both results were not statistically significant. Developmental regression is defined as the loss of a previously established skill. It is estimated that about 30% of patients with ASD will have a developmental regression which typically occurs between 18 and 24 months of age [23].

The presence of epilepsy and/or epileptiform EEG abnormalities has been postulated as a risk factor for regression; however, the data remain conflicting. This is most likely due to the confounding variables related to the patient characteristics in different studies. Many other studies have reported no difference in the rates of autistic regression between children with or without epilepsy [16], while others found that regression is more common in those with epilepsy [24]. Most of these were smaller samples, and the data were not adjusted for the presence of intellectual disability. In a large cross sectional study, autistic regression was reported as more common in those with epilepsy (6.7%) compared to those without (3.6%); however, when the analysis was adjusted for intellectual disability (ID), the difference was no longer significant [25]. In another sample with idiopathic ASD, investigators found no significant difference in the rates of regression between patients with intractable epilepsy and those with controlled seizures [26].

Some motor abnormalities in autism appear to be associated with involvement of the basal ganglia, supplementary motor and anterior cingulate regions [27]. Functional magnetic resonance imaging (fMRI) studies shows atypical activity patterns of cerebral and cerebellar systems in those with autism, despite normal task performance [28]. In our study, autistic patients performed brain MRI showed normal imaging despite of the mild motor delay encountered early during their development.

## Conclusion

Autism is one of the risk factors for epilepsy. In patients with ASD, epilepsy is reported to occur in one-third of patients. Different EEG changes may be present in children with ASD such as slowing, asymmetry, sharp waves or spikes, sharp and slow waves, generalized sharp and slow waves.

Epilepsy may be considered as one of the aggravating factors for behavioural/emotional outcomes for individuals with autism. In ASD, seizures and EEG abnormalities could represent an epiphenomenon of a cerebral dysfunction independent of apparent lesions. Early detection of abnormalities in EEG signals may be an early marker for the development of cognitive impairment in patients with ASD.

## Fund

None

## Conflicts of Interest

None

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