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ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

EEG Findings in Patients with Rett Syndrome

Rett Sendromlu Olgularda Elektroensefalografi Bulguları


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Summary

Objectives: Rett syndrome (RS) is a neurodevelopmental disorder that primarily affects girls and is characterized by microcephaly, regression of language, loss of effective hand use, epilepsy, and electroencephalogram (EEG) abnormalities. This study investigated EEG findings of 12 female patients diagnosed with RS.

Methods: Twelve girls with RS who were treated by İstanbul University İstanbul Faculty of Medicine Department of Neurology were examined clinically and electrophysiologically.

Results: Age of the patients ranged between 3 years, 1 month and 16 years, 8 months. Seizures were present in 9 cases. At time of first EEG, 10 of these patients were in stage II, and 2 patients were in stage III. The first EEG of 5 patients was normal. Six patients, 5 in stage II and 1 in stage III, had central spikes. During the observation period, 4 cases continued to demonstrate central spikes as progression advanced from stage II to III.

Conclusion: Clinicians need to be familiar with RS diagnostic criteria and the staging of this syndrome in order to request appropriate genetic testing. Continued EEG follow-up is helpful in the clinical management of patients with RS as well as for collection of scientific data.

Keywords: EEG; electroencephalography; epileptiform activity; Rett syndrome.

Özet

Amaç: Rett sendromu (RS) esas olarak kız çocuklarını etkileyen, mikrosefali, dilde gerileme, ellerin amaca yönelik kullanımının kaybı, tekrarlayıcı el hareketleri, epilepsi ve elektroensefalografi (EEG) anormalliklerinin sık görüldüğü nörogelişimsel bir hastalıktır. Bu çalışmada RS tanısı almış 12 kız olgunun EEG bulgularının incelenmesi amaçlanmıştır.

Gereç ve Yöntem: İstanbul Üniversitesi İstanbul Tıp Fakültesi, Nöroloji Anabilim Dalı Çocuk Nörolojisi Bilim Dalı'nda takip edilen RS'li 12 kız çocuğu klinik ve elektroensefalografik olarak incelendi.

Bulgular: Olguların yaşları 3 yıl 1 ay–16 yıl 8 ay arasında, (ortalama 7 yıl 1 ay), yakınmalarının başlangıç yaşı 2–24 ay arasında (ortalama 15 ay) idi. Dokuz olguda epileptik nöbetler vardı. İlk EEG incelemeleri sırasında 10 olgu II., 2'si III. evrede idi. İlk EEG'leri normal sınırlarda bulunan beş olgunun dördü inceleme sırasında II., biri III. evredeydi. Başlangıç EEG'leri sırasında beşi II., biri III. evredeki altı olguda santral dikenler saptandı. İzlem süresinde evre II'den evre III'e geçen dört olguda santral dikenler devam ediyordu, ikisinde ayrıca seyrek jeneralize epileptiform deşarjlar vardı.

Sonuç: Rett sendromunun kesin tanısı günümüzde mutasyonun gösterilmesiyle konulmaktadır. Ancak klinisyenlerin genetik incelemeye yönlendirecekleri olguların seçimi için hastalığın tanı kriterlerini ve klinik evrelemesini iyi bilmeleri gerekmektedir. Rett sendromlu olguların EEG incelemelerinin takip süreçleri içinde tekrarlanmasının hem klinik pratikte yardımcı olacağı, hem de bilimsel veri birikimine katkıda bulunacağı kanısındayız.

Anahtar sözcükler: EEG; elektroensefalografi; epileptiform aktivite; Rett sendromu.

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Introduction

Rett syndrome (RS) is a progressive disease especially seen in girls. It progresses with microcephaly, cognitive destruction, loss of receptive/expressive language ability, and intentional hand movements.[1,2] This disease is discussed in the basic sources of pediatric neurology and described under the category of "degenerative diseases".[3] Previously, it was categorized under the heading of common developmental disorders (CDD and autistic spectrum disorder) and removed from the classification at Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[4,5]

The Rett Syndrome Diagnostic Criteria Study Group determined detailed diagnostic criteria of the disease in 1988, and four main clinical stages of the disease were categorized.[6] The general diagnostic criteria for RS include a normal pre-natal, natal, and postnatal development in the first 6 months; a decrease in the normal head circumference 5 months to 4 years after birth; a loss of acquired manual skills (6–30 months); a severe deterioration in receiver and enunciator language skills; severe psychomotor retardation; stereotypic hand movements (twisting, squeezing, taking something to the mouth); apraxia; and ataxia. Intermittent hyperventilation, breath-holding episodes, electroencephalographic (EEG) abnormalities, seizures (occur at stage II and become frequent at stage III), spasticity, bruxism, sleep disorders, peripheral vasomotor problems, and scoliosis support the diagnosis. Damage by birth and metabolic or other progressive neurological diseases are among the exclusion criteria. Pre- and postnatal growth and development is normal in girls with classical RS. When head circumference is normal at birth, a delay period between 3 and -6 months follows and head growth slows down. Subsequently, autistic behaviors and stereotyped hand movements develop. Hypotonia, loss of eye contact, and losing interest in games and the outside environment are observed between 6 and 18 months. A growth retardation occurs due to a decrease in head circumference and body weight after 3 years of age. Although it varies according to the stage of the disease, epileptic seizure incidences, and epileptiform activity in EEG are extremely high in Rett syndrome (RS).[7,8]

Table 1. Clinical stages

Stage I
Early –onset stagnation (onset age: 6–18 months):
Stagnation in development, and head circumference growth
Waning interest in play
Hypotonia
Stage II
Rapid deterioration (onset age: 1–3 years; persists for weeks-months):
Rapid developmental regression
Loss of purpıoseful hand use, and expressive language skill
Midline stereotypic hand movements (hadn wringing, tapping, clapping, mouthing)
Autistic symptoms
Seizures, and/or electroencephalographic bnormalities
Sleep disorder
Serlf-inflicting behaviours (biting fingers, and arm, striking face)
Stage III
Pseudo-stagnation period (onset age: 2–10 yeats; persists for months-years)
Seizures, and stereotypical hand movements (continues)
Severe mental retardation
Decrease in autistic symptoms
Prominent ataxia, apraxia
Hyperventilation, breath holding, aerophagia
Apneic episodes while awake
Bruxism
Spasticity, and early-onset scoliosis
Stage IV
Late-onset motor dysfunction (bage onset: presists for years after 10 years of age):
Nearly complete loss of speech
Upper, and lower motor neuron findings
Progressive scoliosis, muscle atrophy, and rigidity
Decrease in mobilization
Trophic disorder of feet
Rare seizures
Increase in eye contact

Materials and Methods

Twelve girls, who directly visited the pediatric neurology clinic in the Department of Neurobiology at İstanbul Faculty of İstanbul University or were examined in the pediatric mental health and diseases clinic, were included in this study. The cases were evaluated by detailed neurological and psychiatric examinations, and Gesell or Denver developmental tests were applied. Sleep EEGs were taken at least once. Routine blood and urine studies, congenital metabolic disease screening tests, and cranial MR imaging analy-

ses were performed for all the cases in terms of differential diagnosis.

Clinical evaluations

Cognitive and behavioral evaluations, including social relations, verbal and nonverbal communication, interests, and activities, were performed during the psychiatric examination. In the systemic examination, head circumference was measured and checked in terms of presence of deformity, dimorphism, or organomegaly. Although it was quite hard to perform neurological examination in children with RS, the cases in this study were evaluated in terms of posture, balance, walking, use of limbs, possible stereotyped movements, cranial area, tonus, deep tendon reflexes, and basal skin reflex.

Clinical evaluations revealed that all cases met the classic RS diagnostic criteria seen in girls.[6,9] Moreover, a checklist of scoring between 0 and 12 and a cutoff value of 8, which was developed by Huppke et al. and covered the diagnostic criteria of this syndrome (such as normal psychomotor development in the first 6 months, normal head circumference at birth, no hand skills or loss of hand skills, stereotyped hand movements, no language ability acquired, or loss of acquired language), was applied.[10]

Other examinations

Gesell or Denver developmental tests applied to the cases by experienced psychologists to evaluate the language and motor development, as well as personal–social development levels. These tests were translated into Turkish, and their validity and reliability were shown and used in different studies.[11,12]

Routine hematology, biochemistry, and urine examinations, as well as congenital metabolic disease (CMD) screening tests in the Istanbul Medical Faculty, Children's Nutrition and Metabolism Department laboratory were performed for all cases. It is possible to screen a number of metabolic diseases, including phenylketonuria, tyrosinemia, "maple syrup urine" disease, homocystinuria, hyperglycemia, urea cycle defects, methyl malonic acidemia, and multiple carboxylase deficiency by CMD screening tests.

Since it is not possible to perform cranial imaging without applying sedation in children with RS, standard cranial magnetic resonance imaging (MRI) examinations of the cases were performed at different centers where sedation was possible.

Genetic studies of 12 female cases were carried out within the scope of another study at the Boğaziçi University of Molecular Biology and Genetics Department Laboratories, and the genetic diagnosis was confirmed by showing methyl-CpG-binding protein 2 (MeCP2) mutation.[13]

EEG studies were performed at least once or a couple of times during the follow-up (including at least 30 min of sleep time) using a digital EEG device (Medelec DG Compact 32 and Profile; Vickers Medical, Surrey, UK) in the Electro-diagnostic Digital EEG laboratory at the Neurology İstanbul Medical Faculty, Department of Neurology, Electrodiagnostic Neurology Division, Elect All EEGs were visually evaluated by experienced clinical neurophysiologists (S. A., C. G.) in terms of epileptiform and nonepileptiform paroxysmal activities and also for basic activity.

Results

Demographic features

The ages of 12 girls diagnosed with RS varied from 3 years 1 month to 16 years and 8 months. The mean age was found to be 7 years and 1 month. The age at onset of symptoms was 2–24 months (mean 15 months), and the age of visiting the neurology clinic was 1.8–16.6 years (mean 4.5 years).

Medical history features

Nine (75%) cases had epileptic seizure history, and three (25%) cases had no seizure history. Six of these cases had generalized tonic–clonic convulsions, two of them also had additional absences, and tonic–clonic convulsions and myoclonuses were defined in one of the cases. Regarding antiepileptic drugs, four of them used valproic acid, three of them used carbamazepine, one of them used valproic acid and clonazepam, and one of them used valproic acid, clonazepam, and carbamazepine together.

Examination features

Systemic, neurological, and psychiatric examinations and evaluations revealed that all cases met the classical RS diagnostic criteria seen in girls (Table 2).[6,9] The Huppke scoring was higher than the cutoff value for 10 cases, and total scores of both cases were found to be 6 and 7, which were lower than 8. These results were consistent with the litera-

Table 2. EEG results of all the cases

Patient	Age at EEG	Clinical stage	Central peaks	Pseudo-periodic delta discharge	Mono-rhythmic theta activity	Rhythmic gen. peaks	Other	NL/ INL	BA	Nöbet öyküsü	AED
AE	3 years 2 months	II	+						Sufficient		
YB	8 yaş	III	+	+	+		Alpha-like activity		Insufficient	+	VPA
EB	8 years	II	+						Insufficient	+	VPA,
	3 years 3 months	II	+						Insufficient		CBZ, CZP
	8 years 2 months	III	+						Insufficient		
	8 years 10 months	III	+		+ Rare		Rare suppression periods		Insufficient		
YA	3 years 7 months	II		+			Alpha-like activity		Insufficient	+	VPA
	8 years 8 months	IV	+		+				Insufficient		CZP
IA	2 years 1 months	II	+						ALLSL		
	2 years 8 months	II	+						ALLSL		
	4 years 7 months	III	+						Insufficient	+	CBZ
	5 years 7 months	III	+						Insufficient		
EC	3 years	II	+	+					Insufficient		
	5 years 4 months	III	+			+ Rare			Insufficient	+	CBZ
DA	1 years 20 months	II	+						Insufficient	+	VPA
	3 years 2 months	II	+			+ Sometimes			Insufficient		
	5 years	III	+			+ Sometimes			Insufficient		
AC	3 years 8 months	II						NSİ	Sufficient	+	VPA
NT	16 years 9 months	III						NSİ	ALLSL	+	VPA
MP	3 years 8 months	II						NSİ	Sufficient	+	
GNT	2 years 8 months	II						NSİ	Sufficient	+	CBZ
RY	4 years 2 months	II						NSİ	Sufficient		
	6 years 2 months	II						NSİ	Sufficient		

AED: Antiepileptic drug; ALLSL, at lower limit of sufficient level; CBZ: Carbamazepine; INL: In normal limits; NL: Normal; VPA: Valproic acid.

ture stating that Huppke scores of some RS cases with the mutation was below than 8.[14]

Development tests

The results of these tests (Gesell development test, Denver development screening inventory) applied by experienced psychologists were assessed separately for each area by considering the detected language with children's calendar age, socialization, and age of development in the motor fields. The results showed that the cases were developmentally challenged in the indicated areas. These results were consistent with the Huppke scores in most cases.

Routine blood and urine examinations of all cases were within normal limits, and also congenital metabolic disease (CMD) screening tests were normal. Cranial MRIs were normal except a septum pellucidum variation in one of the cases.

EEG analyses

All EEGs were performed during sleep because of the patients' clinical status (lack of cooperativeness and involuntary movements in most cases). The findings are summarized in Table 1.

During the first EEG imaging, 10 cases were diagnosed as stage II and 2 cases were diagnosed as stage III. The first EEGs were found in normal limits for five of the cases (no apparent epileptiform or nonepileptiform abnormalities); the basic activities (BAs) were sufficient (at the lower limit of sufficient level in of one case). One of the five cases was at stage II, and another was at stage III.

During the initial EEGs, central peaks and/or multiple peaks were detected in six cases (five of them at stage II and one of them at stage III) (Figs. 1 and 2). These peaks were central in two cases and centro-temporal in four cases. Also,

some pseudo-periodic delta discharges and slow wave series at 3–3.5 Hz Frequency, which lasted 10–15 s in the frontal regions were detected in the case at stage III. Also, an alpha-like activity, which lasted 3–4 s was observed in frontal areas. During these first EEG analyses, BAs in two of the five cases at stage II with central peaks were sufficient and it was found as insufficient in three of the cases. The BA of the case at stage III with central peaks at the first EEG was insufficient.

When the first EEG was performed for one of the cases at stage II, central peaks were found, but some pseudo-periodic delta discharges and an alpha-wave-like activity, which was actually a pattern of awakening, were observed (Fig. 3). In the EEG of the same case at stage IV, some multiple-peak slow waves in both fronto-central regions and some slow wave series at 3.5–4 Hz frequency lasted almost 30 s were detected in the same region (Figs. 4a and b). The basic activities (BAs) of this case in two different EEG periods were insufficient.

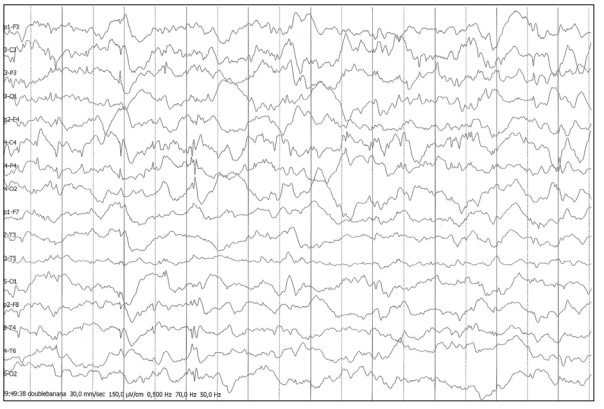

Fig. 1. IA, 2 years 8 months, clinical Stage II: sleep EEG of IA when he/she had no seizures: generally independent multiple spike-slow waves in both central regions (the one that makes phase comparison at C3 and C4 electrode positions).

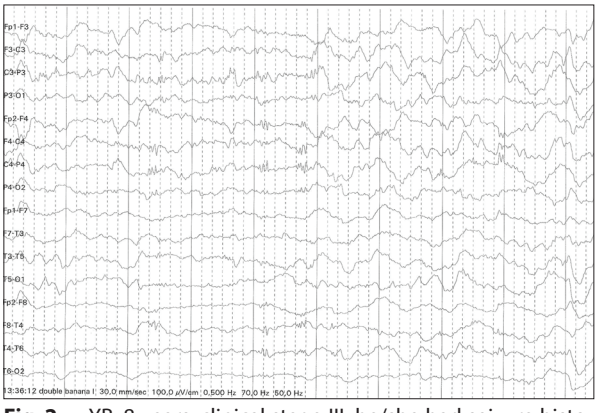

Fig. 2. YB, 8 years, clinical stage III: he/she had seizure history; multiple peaks in both central regions of the sleep EEG.

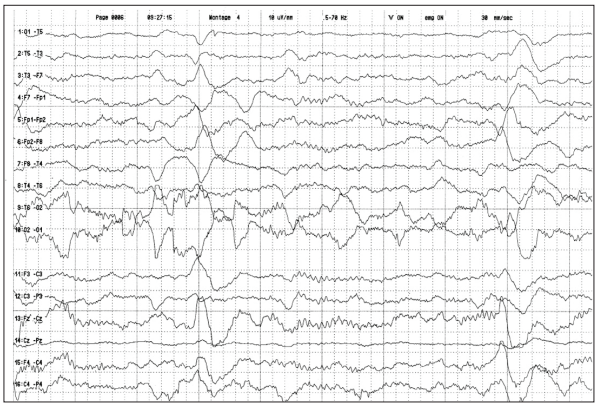

Fig. 3. YA, 3 years 7 months, clinical stage II: he/she had seizure history; no central peaks in the sleep EEG, but pseudo-periodic delta discharges and alpha-like activity were observed.

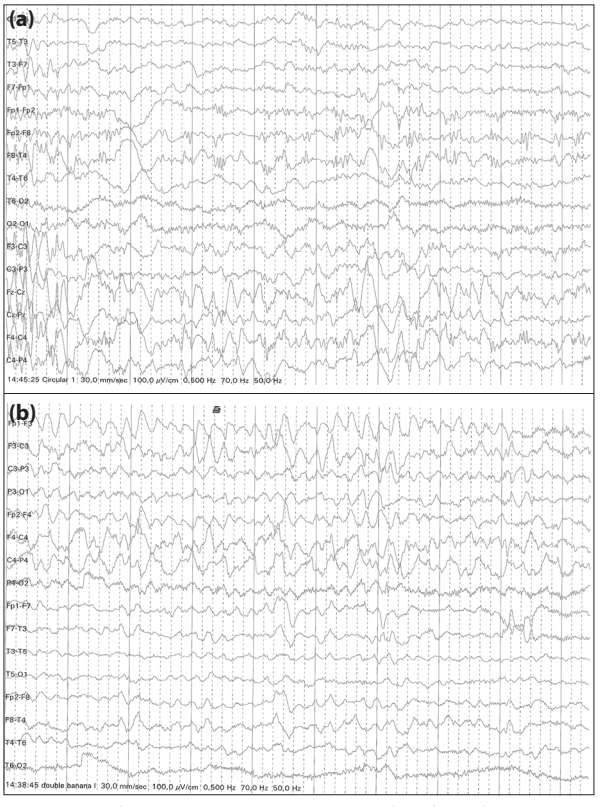

Fig. 4. **(a, b)** Same case, 8 years 8 months, clinical stage IV: In his/her sleep EEG, multiple peaks and 3.5- to 4-Hz slow wave series, which lasted almost 30 s, were observed in both fronto-central regions.

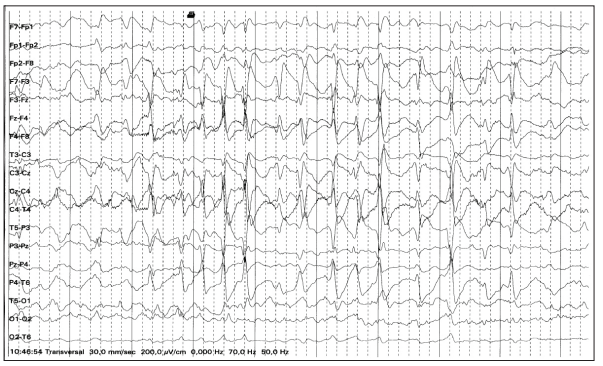

Fig. 5. EB, 8 years 10 months, clinical stage III: Nearly continuous, high-amplitude spike-slow waves in the fronto-centro-parietal regions of the sleep EEG during the period when no generalized convulsive seizures were observed for 6 months and myoclonuses were noted.

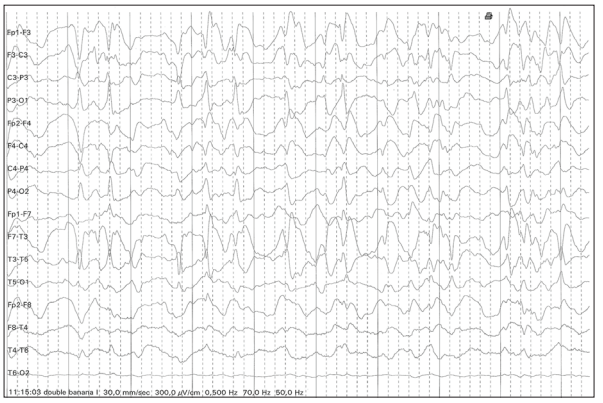

Fig. 6. One of the suppression periods observed several times in both hemispheres in the same EEG of the same case.

During the follow-up, it was observed that the central peaks continued in four cases from stage II to R. In two of these cases, some rare generalized epileptiform discharges were also observed. In one case, epileptic activities were observed in the fronto-centro-parietal regions as almost continuous, high-amplitude spike-slow waves (Fig. 5). Several periods of suppression were also seen in this EEG record of the case (Fig. 6).

A tactile stimulation (in the form of small strokes in the forearm) was applied to two cases at stage II during EEG. In one of the stimulations applied to the right or left forearm simultaneously, sharp waves were observed in the right temporal region (T4 electrode position) at the same time in the EEG. In the other case, no similar activity occurred during the tactile stimulation. In this case, it was observed that the central peaks of the EEG were suppressed several times with the passive movement of the index finger, but these peaks sometimes disappeared spontaneously.

Discussion

A number of neuropathological, neurochemical, and morphometric brain imaging studies have been performed in recent years on the etiology of RS.[15,16] The genetic basis was clarified in 1999 by demonstrating mutations in genes encoding the MeCP2 in the Xq28 region.[13] Today, this disease is diagnosed by showing the mutation; however, it is important to have a good understanding of the diagnostic criteria and the clinical stage to select the cases for genetic investigation.

The ages of 12 female patients diagnosed with RS ranged from 1 year to 16 years and 8 months, and the average age was found to be 7 years and 1 month. Genetic studies of all female cases were performed within the scope of another study, and all of the cases were shown to be positive in terms of MeCP2 mutation.

Among the supportive criteria for diagnosis, epileptic seizures were seen in 50%–90% of patients with RS, and antiepileptic drugs (AEDs) were commonly used in this syndrome.[2,7,17–19] Epileptic seizure history was present in nine (75%) of the patients in the present study; this ratio was within the values specified in the other series. Genetic tonic–clonic convulsions were identified in six of nine cases with seizure history, additional absences were present in two of the cases, and generalized tonic–clonic convulsions and myoclonus were present in one of the cases. Regarding antiepileptic drugs, four of the cases used valproic acid, three of the cases used carbamazepine, one of the cases used valproic acid and clonazepam, and one of the cases used valproic acid, clonazepam, and carbamazepine. Despite not being a large series, it is reported that treatment in RS patients with epileptic seizures was not different from that in nonepileptic individuals.[7]

RS cases show a great diversity in behavior. Several behavioral changes such as episodes of breath holding or hyperventilation, sometimes stereotyped hand movements that may be continuous, and idle-absent stares accompanied by sudden absence-like stop-motion activity may be interpreted as seizure by the patient's relatives. Epileptiform discharges were not detected in the EEG trace during episodes with changes in respiratory rhythm (breath holding, hyper-

ventilation, and so forth) or recurrent hand movements (8). Therefore, conducting similar studies with video-EEG analyses might be useful in adding value to the present study findings.[8,20,21]

Despite no specific EEG patterns for RS, some electrographic abnormalities, varying according to the clinical stages of this disease, have been described.[7,8] EEG results, regardless of the presence or absence of seizures, were among the supportive diagnostic criteria established in 1988.[6] In stage I, it is known that EEGs of the cases are typically normal in sleep, and a mild deceleration may be observed in EEGs during wakefulness. [7,8] No stage I case visited the clinic in stage I in this study.

In stage II, mild slowing in BA is observed initially. A mild–moderate slowing in BA occurs with the disappearance of alpha waves in the occipital regions later. Little or no phasic elements of non-rapid eye movement (NREM) were observed in sleep. In this phase, NREM also has focal peaks or sharp-slow waves in the central and temporal regions, followed by generalized spike-slow wave discharges in the sleep and then in the wakefulness.[7,8] During the first EEGs, central peaks and/or multiple peaks were detected in five stage II patients and one stage III patient in a total of six cases. The peaks were central only in two cases and observed in the centro-temporal regions in four for the cases. BA was found to be sufficient in two of the five cases and insufficient in three of the cases at stage II. The cases had central peaks at the conducting EEG analyses. BA was insufficient in the case at stage III that had central peaks in the first EEG. These results were consistent with the previous results stating that the central peaks occurred at stage II and a deceleration was observed in BA.[7,8,22]

In stage III, the EEG became worse. The moderate deceleration in BA is observed during wakefulness; the phasic elements of the NREM can be either hardly distinguished or absent. Generalized and slow wave activities with focal and multifocal peaks or sharp-slow waves are usually seen in sleep and awake modes.[7,8,22] The present study found that the central peaks continued in the four cases passing from stage II to stage III during the follow-up period. In two of these cases, some rare generalized epileptiform discharges were also observed in sleep. These data were similar to those in the other studies mentioned earlier (the continuation of the central peaks in phase III and the appearance of generalized discharges in sleep).

The cases with RS had significant psychomotor retardation at stage IV, and their occipital dominant rhythms (alpha waves) in EEGs are lost. Also, severe deceleration in theta and delta frequency waves occurs. Sleep spindles and vertex sharpness are not observed in NREM. Focal and multifocal spikes or sharp-slow waves and generalized slow-throbbing–slow wave activity occur in both sleep and awake modes. However, it has been pointed out that EEGs are assessed within normal limits (less pronounced deceleration in BA) in few parts of stage IV in some cases, and no waking and epileptiform abnormalities were observed in sleep, either.[7,8]

It has been reported that EEGs performed during the chronic period of the disease have a rhythmic activity at the frequency of 5–7 Hz, which is called monotone tetra rhythm. This activity is observed in the bilateral central regions during the early chronic period and later in a more generalized manner.[23,24] Also, it has been reported that irregular bilateral discharges composed of delta waves with high amplitude and pseudo-periodically occurring in a mixed state with low-voltage BA during sleep and awake modes can be seen at a later stage such as stage IV. Sometimes a relative suppression in BA after these discharges can be observed.[8,22]

Some pseudo-periodic delta discharges were observed in both cases with central peaks at stages II and III, respectively, in the present study. In the case at stage III, an alpha wave-like activity, which lasts 10–15 s with slow wave sequences at the frequency of 3–3.5 Hz and 3-4 s in the frontal areas followed by occipital regions with closed eyes, was observed. Central peaks were not present in the case at stage II when the first EEG was performed. In the EEG of this case at stage IV, multiple-peak slow waves in both central regions and some slow wave series at 3.5–4 Hz lasting almost 30 s were detected in the same region. In another case at stage III having central peaks, several episodes of suppression were observed without pseudo-periodic discharges during EEG analyses. Although no significant behavioral differences were observed in these patients during the suppression periods, it was concluded that video-EEG examinations were necessary in these cases. Several studies have reported that the resulting peaks are simple, stereotypical, and biphasic, in which spikes occur in spontaneous central spines on EEGs, and the stimulation of discharges on the hemisphere with small strokes of the hand is attempted.

If a peak occurs in the opposite hemisphere, the patient is described as "sensitive to touch".[25,26]

A tactile stimulation (in the form of small strokes on the forearm) was applied to two cases at stage II during EEG. In one of the stimulations applied to the right or left forearm simultaneously, sharp waves were observed in the right temporal region. In the other case, no similar activity occurred during the tactile stimulation. In this case, it was observed that the central peaks of the EEG were suppressed several times with the passive movement of the index finger, but these peaks sometimes disappeared spontaneously. In the studies showing the emergence of peaks at stage II in the opposite hemisphere with the tactile stimulus, it has been interpreted that transmitting "afferent" pathways affected by diseases to the cortex may cause an abnormal response similar to EEG-peak activity.[18,24] Another study reported no evidence that this type of sensitivity affected the clinical outcome.[27] Another report emphasized that this type of response did not occur in the majority of children with RS.[28] All of 12 female cases met the diagnostic criteria in this study and were also confirmed by MeCP2 mutations; the first EEGs of five cases were within normal limits. Although four of the cases were at stage II and one of the cases was at stage III, not all samples were evaluated by the same individual. It is remarkable to detect epileptiform and nonepileptiform anomalies in the EEGs of the cases. In some studies at stage IV, it has been reported that EEGs are within normal limits (instead of stages II and III) in a few cases and no epileptiform abnormality is observed in sleep and awake cycle.[7,8] In the majority of cases at stage IV, some e psychomotor problems and BA impairment in EEGs with severe epileptic activities were seen. Future studies should 'aim to have a sufficient BA in these cases.

Conclusions

The exact diagnosis of Rett syndrome is now made by showing mutations. Clinicians need to be well informed about the diagnostic criteria and clinical stage of the disease to select the cases for which they would like to perform genetic testing. Supportive diagnostic criteria include epileptic seizures with a frequency of 50%–90% and EEG abnormalities. Due to EEG anomalies with variable and sometimes rare findings depending on the circumstances, it is believed that the recurrence of RS cases in the follow-up process of EEG studies might contribute to clinical practice and scientific data accumulation.

Conflict of interest

None declared.

Authorship contributions

Concept: S.A., A.E.Ö., C.G.; Design: S.A., C.G., A.E.Ö.; Data collection &/or processing: S.A., C.G., Z.Y.; Analysis and/or interpretation: S.A., C.G.; Literature search: S.A.; Writing: S.A.; Critical review: A.E.Ö, C.G., M.E.

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