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Original Article

Evaluation of seizures and clinical features of pediatric patients diagnosed with Rett Syndrome who were detected to have MECP2 mutation

MECP2 mutasyonu saptanan Rett sendromu tanılı pediatrik hastalarin klinik ve nöbet özelliklerinin değerlendirilmesi

Serkan KIRIK*, Mahmut Aslan, Bilge OZGOR, Serdal GUNGOR

Inonu University, Faculty of Medicine, Department of Pediatric Neurology, Malatya,/TURKEY

Abstract

Aim: The aim of this study was to investigate the seizures and clinical characteristics of patients diagnosed with Rett syndrome with MECP2 mutation who were followed up in our tertiary pediatric neurology clinic.

Material and Methods: Patients who were admitted to the pediatric neurology clinic of Inonu University Faculty of Medicine between 2010 and 2015. The patients got MECP2 mutation and whose electronic medical datas were available, were included in our study. Electroencephalography (EEG) records of the patients and antiepileptic treatments they received were evaluated.

Results: The mean age of the patients was 10.2 (9.36 ± 2.75) and the mean age at onset of complaints was 15 months (12.1 ± 5.19). Six of 9 patients who had seizures had generalized tonic clonic seizures and three patients had focal seizures. The most preferred antiepileptic drug was valproic acid.

Conclusion: Rett syndrome characterized with cognitive detoration, epileptic seizures, and microcephaly. Increased awareness provides early diagnosis and suitable treatment for female patients applied with otism and microcephalia in particular, and it is also important for preventing unnecessary diagnostic tests.

Keywords: Rett syndrome, MECP2 mutation, pediatric, epilepsy

Corresponding author*: Serkan KIRIK, Inonu University, Faculty of Medicine, Department of Pediatric Neurology, Malatya,/TURKEY
E-mail: srknkrk@hotmail.com
ORCİD: 0000-0002-8658-2448
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Öz

Amaç: Bu çalışmanın amacı üçüncü basamak pediatrik nöroloji kliniğimizde izlenen MECP2 mutasyonu saptanan Rett Sendromu tanılı hastaların nöbetlerini ve klinik özelliklerini araştırdık.

Gereç ve Yöntemler: Çalışmamıza İnönü Üniversitesi Tıp Fakültesi çocuk nöroloji kliniğine 2010-2015 yılları arasında başvuran ve MECP2 mutasyonu saptanan ve dosya verilerine ulaşılan hastalar dahil edildi. Hastaların elektroensefalografi (EEG) kayıtları, almış oldukları tedaviler değerlendirildi.

Bulgular: Hastaların yaş ortalaması 10,2 (9,36 ± 2,75) ve şikayete başlama yaşı ortalama 15 ay (12,1 ± 5,19) idi. Nöbet geçiren 9 hastanın altısında jeneralize tonik klonik nöbetler ve üç hastada fokal nöbetler vardı. En çok tercih edilen antiepileptic ise valproik asitti.

Sonuç: Rett sendromu bilişsel gerilik, epileptic nöbetler, mikrosefali ile karakterize bir durumdur. Artan farkındalık, özellikle otizm ve mikrosefali ile başvuran kız hastalara erken tanı ve uygun tedavi sağlarken, tanı için gereksiz testlerin yapılmasını da önler.

Anahtar kelimler: Rett sendromu, MECP2 Mutasyonu, Pediatrik

Introduction

Rett syndrome is a neurodevelopmental disorder identified with early neurological regression following normal development stages and nearly always seen on female patients. It was identified on 1966 by an Austrian pediatrician, Andreas Rett [1]. It is observed to have similar prevalence in all communities, which is approximately once in 15.000-20.000 live female births [2]. Patients are mostly born on time after a normal pregnancy. It is a genetic disease accompanied by loss of cognitive, verbal, fine-gross motor skills and communication, autonomic dysfunction, and frequent seizures [1].

Clinical course of Rett syndrome is examined in four phases [3]. The first phase, early-onset stagnation phase is observed between months 6-18, it is characterized with sudden changes in communication behavior of the infant and decrease in its interest to environment. Seizures are observed after year 1, especially around age 2 with the rapid destructive phase [3, 4]. Epileptic seizures have been reported on literature with various frequency between 60%-94%. In general, generalized tonic, tonic- clonic, and to a lesser extent, focal seizures are observed. Epileptic seizures may be confused with stereotypical movements frequently observed in patients and they may not be identified, for this reason electroencephalography (EEG) is an important tool on their distinction from non-epileptic behavioral movements. EEG findings of patients are often similar to four clinical phases of the disease. Nonetheless, EEG results are not characteristic for Rett syndrome [1, 4].

Mutations in MECP2 gene (OMIM#300005) are used the pathogenesis of Rett syndrome. MECP2 protein is present in high levels especially in the brain. Inactivation mutations in MECP2 gene results in improper and overexpression of genes that are not required to be expressed, and this causes negative effects on the maturation of central nervous system.

The purpose of this study was to contribute in literature by the evaluation 9 female patients diagnosed with Rett syndrome by detecting the mutation in MECP2 gene, with regard to the characteristics of epileptic seizures, EEG, treatment response and neuro-imaging methods.

Material and Methods

This study was performed by the retrospective evaluation of patients who have applied to Inonu University Faculty of Medicine Department of Pediatric Neurology Clinic between years 2010-2015. Genetic screening results for the MECP2 gene of 9 female patients living in the Eastern region of Turkey. Starting age of the stereotype, the frequency of seizures, types of seizures, mental retardation, head circumference and magnetic resonance imaging (MRI) results were reviewed in the study.

Peripheral blood samples were obtained from patients after they signed an informed consent forms for genetic investigation. Genomic DNA was isolated from venous blood by using kit (Qiagen, Germany) according to manufacturer's protocol. Direct sequencing of the coding exons of MECP2 gene was made for patients. An initial denaturating step of 95°C for 2 min. was performed, followed by 95°C for 30 sec,56°C for 30 sec. and 72°C for 50 sec, followed by 30 cycles at 95°C for 30 sec and 72°C for 50 sec .All reactions terminated by a final elongation step at 72°C for 5 min. The amplicons have been analyzed by direct sequencing with ABI Prism (Life Technologies, USA).

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We classified epileptic seizures according to the 2017 International Classification of Seizures, proposed by ILAE in 2017 [5].

This study was approved by local ethical committee. Informed consent was obtained from all patients and the principles of the Helsinki Declaration were followed.

Results

Average age of patients was 10,2 years old (9,36±2,75) and starting age for complaints was 15 months on average (12,1±5,19). Six of 9 patients with seizures had generalized tonic clonic seizures, and three patients had focal seizures. Patients who received two or more antiepileptic treatments were identified to have refractory epilepsy. Seizures were refractory in four of these 9 patients. Two of 4 patients with refractory seizures suffered seizures once a week, and other 2 patients had seizures once a month and/or more. Most commonly used anti-epileptic was valproic acid. Benzodiazepine was preferred in the combination therapy of all patients with refractory seizures. Most common anomaly in EEG was generalized epileptic anomalies (4 patients). Mutations, EEG results and used medications are presented in Table 1. This choice was due to clinician's preference according to clinical characteristics of patients.

Table 1. EEG, seizure pattern and antiepileptic drugs of patients

Patient	MECP2 Mutation	Type of seizure	Frequency of seizure	Drug resistant seizure	AED choice	EEG
1	R255X	GTC	4 in monthly	+	VPA-BZD	Multifocal
2	R255X	Focal	1-2 in monthly	+	VPA-BZD	Focal
3	R270X	Focal	1-2 in monthly	+	TPM-BZD-LAM	Focal
4	R168X	GTC	< 1 month	-	VPA	GED
5	R255X	Focal	< 1 month	-	VPA	Focal
6	R168X	GTC	4 > month	+	VPA-BZD-LEV	GED
7	T158M	GTC	1 in monthly	-	CBZ	GED
8	R133C	GTC	1 < month	-	LEV	GED
9	R168X	GTC	1 < month	-	VPA	GED

AE: Antiepileptic Drug GTC: Generalized tonic-clonic, VPA: Valproic acid, CBZ: Carbamezapine, BZD: Benzodiazepine, LEV: Levetiracetam, TPM: Topiramate, LAM: Lamotrigine, GED: Generalized epileptiform discharges

All patients had mental retardation and stereotype. While head circumference of 8 patients was ≤-2 SD, head circumference was in normal range in 1 patient. All patients underwent neuroradiological imaging. There were no pathological findings in the imaging of six patients. One patient had ischemic non-specific changes, and 2 patients had corpus callosum hypogenesis. Most common MECP2 mutations were R168X and R255X which were detected in three patients.

Discussion

After Rett syndrome was identified by Andreas Rett [1], mutations at Xq28 branch of MECP2 gene were described in detail on 1999. Its characteristics consist of stereotypes and epileptic clinical symptoms with early onset neuromotor development retardation. However, differentiation of stereotype and non-epileptic events from epileptic activities, and starting proper treatment on early period are important [1-3].

It was reported that seizures may lead to serious disturbance in hand skills, ambulation and verbal communication in Rett syndrome cases with epilepsy. According to normal population, seizures in early period are more common. While most commonly reported types of seizures are generalized tonic-clonic and partial seizures, tonic-myoclonic, absence and clonic seizures are observed to be more rare [6, 7]. Studies demonstrate that the frequency of focal seizures and generalized seizures varies. Seizures become more apparent in the third stage of the disease. Early stage EEG findings may be normal, but with advancing stages, focal epileptic, multifocal epileptic and generalized epileptic anomalies may be detected. There are articles reporting refractory seizures in nearly half of patients [8]. In many studies, valproic acid, benzodiazepines, carbamezapine and lamotrigine have been reported as most common treatment choices. While decreased frequency of seizures up to 75% has been reported with valproic acid, only 6% of patients has been reported to be seizure-free [9, 10]. In our study, valproic acid was the preferred antiepileptic in both patients with generalized seizures and patients with focal seizures. Seizure type was generalized tonic clonic seizures in six patients. Three patients had focal seizures. Patients who received two or more medical treatments were identified to have refractory epilepsy. Benzodiazepine was preferred in all patients with refractory seizures. Different from other studies, carbamezapine was preferred in 1 patient with focal seizures in

our study. Levetiracetam, a new generation antiepileptic, was preferred in 2 patients. Two patients were using 3 antiepileptics, two patients were using 2 antiepileptics, and 5 patients were using a single antiepileptic. No difference was determined in mutations with regard to seizure type and treatment response. In seven patients, number of seizures reduced below 50% after antiepileptic treatment. Two patients had at least 1 seizure in a week and they did not benefit from monotherapy.

Although sensitivity of electroencephalography (EEG) has been reported up to 80% in some articles, specificity is low. The common opinion on EEG is that it supports the diagnosis. Hipsarrhytmia and periodical pattern are very rare in EEG [9, 10]. EEG images performed before the start of seizures are generally normal. Electroencephalography results show similar properties in various stages [9]. Electrophysiological results are particularly important in Rett syndrome, in which stereotype and non-epileptic events are frequently observed [10, 17]. In our study, refractory seizures were present in 66,6% of patients with focal epileptic activity, 1 patient with multifocal epileptic activity, and 40% of patients with generalized epileptic activity. This was equal to 55.5% of all patients. Focal epileptic activities were common in central areas.

Tarquinio et al. [4] have stated in their study that there is a characteristic retardation in head circumference percentile of Rett syndrome patients that becomes apparent after age 1, and regular follow-up of head circumference is important. In our study, 8 of 9 patients had microcephalia (< -2SD).

From a clinical aspect, patients are divided in 4 clinical phases. Findings in Phase 1 are stagnation in head circumference and neuromotor development around 6 months. With advancing stages, clinical symptoms become worse. Phase 4 is late motor deterioration phase (starts after age 10, lasts for years); near to complete loss of speech, upper and lower motor neuron findings and Progressive scoliosis, muscle atrophy and rigidity, and decreased mobilization are observed. Stereotypical hand movements such as clapping, scrubbing, rubbing, washing, hitting, bringing hands into mouth, bending fingers and squeezing, which are performed particularly in the middle line, are one of the characteristics of the disease and they appear in phase 2 [2, 3]. All of the patients had the stereotype in our study. One of the patients was in phase 2, 5 patients were in phase 3, and 3 patients were in phase 4. Three patients underwent EEG in pre-seizure period, and only 1 patient had no additional pathology apart from paroxysmal anomaly.

Data on neuro-imaging results are limited in Rett syndrome. In addition, no disease-specific imaging results have been reported [1, 3]. Brain MRI results were normal in six patients, and 2 corpus callosum anomalies were detected in 2 patients (dysgenesis).

MECP2 mutations are detected at 95% rate in classic Rett syndrome, and at 75% in atypical Rett syndrome [11]. There are more than 1000 MECP2 mutations that may be associated with Rett syndrome [12]. However, R106W, R133C, T158M, R168X, R255X, R270X, R294X, R306C mutations are frequently detected in patients. These mutations are responsible for up to 70% of cases [13, 14, 16, 17]. In our study, GTC seizures were determined in 3 patients with R168X mutation. One of these patients was refractory to treatment, and seizures in other two patients were controlled with a single medication. R255X mutation was detected in 3 patients, and this corresponded to 2 of 3 patients with focal seizures. Two of patients with R255X mutation did not benefit from monotherapy. A patient with R255X mutation had refractory epilepsy.

Consequently, there is a small number of pediatric studies performed on Rett syndrome and EEG results. In particular, this study has the feature of being one of the first pediatric studies performed on seizures and electrophysiological characteristics by the identification of MECP2 mutations. Performance of future studies with a higher number of patients and clinical characteristics may present more information on electrophysiological results and mutations.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest

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