Case Report

Late-Onset Myoclonic Epilepsy in Down Syndrome: Investigation of EPM1 Gene Mutations in two Cases

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Abstract

Late-onset myoclonic epilepsy is being increasingly recognized as a late complication in elderly patients with Down syndrome (DS) in association with cognitive decline. This specific syndrome bears some broad clinical and EEG similarities to the progressive myoclonic epilepsies, particularly Unverricht-Lundborg disease (ULD). Our aim was to investigate a possible shared patho-genetic mechanism for clinico-physiological similarities in these different genetic syndromes. Two patients diagnosed with DS and late-onset myoclonic epilepsy were included in the study. Dodecamer repeats and other possible CSTB gene mutations were investigated after isolation of DNA from their blood samples. No dodecamer repeats and point mutations could be found. Our study did not show any mutations of EPM1 gene on chromosome 21 but these findings could not exclude a shared genetic mechanism in these syndromes.

Keywords: Down syndrome, epilepsy, myoclonus, EEG, dementia

Down Sendromunda Geç Başlangıçlı Miyoklonik Epilepsi: İki Olguda EPM1 Gen Mutasyonunun Araştırılması

Özet


Anahtar Kelimeler: Down sendromu, epilepsi, miyokloni, EEG, demans
INTRODUCTION

Trisomy 21, or Down syndrome (DS), is a relatively common genetic condition with an incidence dependent on maternal age. The incidence of dementia in DS is estimated to be greater than 25% in individuals over 35 years of age.\(^3\) This number has been shown to increase with advancing age, presumably in relation to the increased probability of triplication and over-expression of the amyloid precursor gene on chromosome 21.\(^{13,14}\) Nearly all patients with DS after the age of 40 years have histopathological evidence of central neurofibrillary proteins, identical to those seen in Alzheimer Disease (AD).\(^{15}\) In this subset of patients with DS, a new entity called as late-onset myoclonic epilepsy was reported and is being increasingly recognized.\(^{1,11,12}\) This specific syndrome bears some broad clinical and EEG similarities to the progressive myoclonic epilepsies, particularly Unverricht-Lundborg disease (ULD). Interestingly, both CSTB (EPM1) gene for ULD and amyloid precursor protein (APP) gene, which is implicated in AD, are located on chromosome 21. The neurobiological mechanism underlying myoclonus in elderly patients with DS is not known. Our aim was to explore for a shared pathogenetic mechanism for the clinico-physiological similarities in these different genetic syndromes.

METHODS

1. Patients

Two patients diagnosed with DS and late-onset myoclonic epilepsy were included in the study. After obtaining written informed consent from their legal custodian, blood samples were taken. Dodecamer repeats and other possible EPM1 mutations on chromosome 21 were investigated after isolation of DNA from their blood samples.

2. Cystatin B (CSTB) Gene Analysis

Genomic DNA was isolated from EDTA preserved whole blood using MagNA Pure DNA Isolation Kit (Roche) in a MagNA Pure Compact (Roche Life Sciences) as described by manufacturer. For both patients, coding sequence of EPM1 (CSTB) gene and exon/intron boundaries were amplified with specific primers and amplified by Polymerase Chain Reaction (PCR) (Primer sequences may be provided upon request). Amplified PCR products were sent to Macrogen Inc. (South Korea) for purification and Sanger Sequencing. Chromatographs were analyzed using CLC Main Workbench 7.0.2 software.

Dodecamer repeat expansion in approximately 200bp upstream of CSTB gene was analysed by Gendia inc.

RESULTS

1. Case 1

A 53-year-old man with DS and a history of progressive cognitive decline over the last four years, predominantly in language abilities and with dependence on caregivers for daily living activities such as dressing and eating, was evaluated because of his first generalized tonic clonic seizure in emergency department. It was reported that myoclonic seizure, characterized by brief, intense, single extremity or whole body jerks had been occurring since the onset of cognitive decline 2.5 years ago, and were first noted during an antibiotic treatment of a pulmonary infection. These jerks were prominent in the mornings and could mostly be provoked by sound. There was no apparent loss of consciousness and the patient continued his activities after the jerks. Diabetes mellitus and bradycardia were also present in his past history. He has a permanent pace-maker placed because of severe bradycardia. Ataxia and urinary incontinence together with severe cognitive decline and frequent, severe myoclonic jerks were observed on neurological examination. Cranial CT...
showed prominent cortical atrophy and enlargement of ventricles compared to his previous cranial MRI which was done 2 years ago (Figure 1a-b-c-d). Progression of these neuroimaging findings were also correlated with deterioration in his neurological status. Focal epileptiform abnormalities over the left frontal region with generalized slowing were found on his EEG recordings (Figure 2a-b). After initiation of levetiracetam and valproate, myoclonic seizures were partially controlled but cognitive deterioration was continued to progress and at the four years of follow-up, the patient was bed-ridden.

2. Case 2
A 58-year-old man diagnosed with DS with a history of frequent myoclonic seizures over the past 7 years was evaluated in our outpatient clinic. Myoclonic seizures had begun after the onset of cognitive decline similar to the first patient. He had been bed-ridden with severe cognitive deterioration and walking difficulty for three years. His EEG revealed focal epileptiform abnormalities over the frontal regions with generalized slowing. Myoclonic seizures were partially controlled with valproate and levetiracetam.

3. Results of genetic analysis
Coding region and exon/intron boundaries of CSTB gene were amplified in total of three amplicons and analyzed by Sanger sequencing for any sequence alterations. No sequence variations were identified.

It is well-known that the main mutation in ULD is an expansion of a dodecamer repeat (CCCCGCCCCGCG) in the 5' flanking area of the CSTB gene.\(^{(6)}\) In the healthy population this dodecamer sequence has two or three copies; for some rare portion of the healthy population this copy number can increase up to 17 repeats. However 90% of all ULD patients have more than 30 repeats in one of the alleles. When our two patients were evaluated for dodecamer repeats by southern blot technique, results showed the presence CSTB repeats in the normal range (2-17 repeats).

![Figure 1a-b-c-d: More prominent atrophy and enlargement of ventricles were detected in cranial CT (1c-d) compared to previous cranial MRI which was done 2 years ago (1a-b). Progression of neuroimaging findings was also correlated with progression in his neurological status.](image-url)
DISCUSSION
Both of our elderly patients with DS had a similar late-onset myoclonic epilepsy syndrome characterized by segmental and massive incapacitating myoclonic jerks, predominantly after morning arousal, following onset of progressive and global cognitive decline. In both cases, myoclonic seizures were partially controlled with valproate and levetiracetam, but cognitive deterioration was continued to progress.

Epilepsy is recognized as a significant cause of additional handicap and morbidity in DS. Some other specific forms of epilepsy may be found with a high prevalence at various ages in DS, including infantile spasms, and reflex seizures. Due to the increased number of elderly DS patients, likely as a consequence of increasing quality of medical and social care, some late-onset complications of this condition including dementia and a specific type of myoclonic epilepsy are being increasingly observed. First described by Genton and Paglia in 1994, as ‘senile myoclonic epilepsy’ this peculiar condition has also been reported as “late-onset myoclonic epilepsy in DS” by Li et al. and Möller et al. in 1995 and in 2001, respectively.

Late-onset myoclonic epilepsy in DS should be suspected in individuals with DS over the age of 35 years. Dementia may precede the onset of myoclonic jerks by months to years, similar to our patients. It is intriguing to note that EPM1 gene for ULD, the prototype of progressive myoclonic epilepsies, and APP gene implicated in AD are both located on
chromosome 21, which was triplicate in DS.\(^{(8)}\) In late stages of DS, myoclonus progresses and may become the most characteristic epileptic symptom as ULD. The exact mechanism underlying myoclonus in DS is not clearly understood like that in ULD. It has been hypothesized that structural abnormalities and biochemical aberrations of the central nervous system (CNS) may be responsible.\(^{(4)}\) Electrophysiological studies indicated that myoclonic seizures are produced through a cortical generator leading to a hyper-excitability of CNS.\(^{(2)}\) Several authors have observed a lower brain neural density and abnormal neuronal distribution, particularly in cortical layers II and IV in DS patients and dysgenesis of dendritic spines in the form of longer and thinner necks, as well as hyper-excitable membrane properties in cultured dorsal root ganglion neurons from fetuses with DS.\(^{(7)}\) Therefore, myoclonus in these patients could theoretically be caused by a combination of several factors, such as modifications of cellular membranes to hyper-excitability, structural modification, and alteration of inhibitory transmission.

**CONCLUSION**

We believe that elderly patients with DS should be evaluated with particular attention to the presence of myoclonic jerks, which may cause injuries. Our findings showed that these seizures could be partly controlled with appropriate treatment. Although we are not able to show any mutations of EPM1 gene on chromosome 21, our findings did not exclude a role of some overlapping genetic mechanism in these syndromes. Extra genes on the third copy of chromosome 21 or epigenetic factors may play role in this distinct type of epilepsy in DS.

**REFERENCES**