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Case Report

Neuronal ceroid lipofuscinosis type-11 in an adolescent

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Abstract

Neuronal ceroid lipofuscinosis (NCL) is a group of progressive neurodegenerative disorders characterized by intracellular accumulation of ceroid lipopigments. Based on gene defect of NCL-associated proteins, 14 types of NCL have been described till date. NCL type 11 was first described in 2014 in two siblings as adult-onset NCL and was found to be due to a homozygous progranulin gene mutation. These siblings had progressive retinopathy, recurrent generalized seizures, moderate ataxia and subtle cognitive dysfunction. Palinopsia was present and MRI showed selective and severe cerebellar atrophy which was progressive with age. There have been no further reports of NCL 11 in literature. We here present a 14-year old girl born to second degree consanguineous couple who presented with gradually increasing frequency of seizures for the past 1 year without any signs of visual abnormalities and dementia. She had an elder sister who had progressive seizures and dementia from 8 years of age and died after few years. Her electroencephalogram showed frequent generalized epileptiform discharges and magnetic resonance imaging (MRI) showed pure cerebellar atrophy mainly affecting the vermis. MRI findings suggested a neurodegenerative disorder like NCL and prompted us to go for whole exome screen which revealed NCL type 11 due to homozygous mutation c.912G>A (p.Trp304Ter) in exon 9 of GRN gene (OMIM#614706). To the best of our knowledge this is the third case of NCL 11 and the first from Asia.

Keywords: Progranulin; Neuronal ceroid lipofuscinosis; CLN11; Cerebellar atrophy

1. Introduction

Neuronal ceroid lipofuscinoses (NCLs) are a group of inherited progressive neurodegenerative characterized by accumulation of ceroid lipopigment mainly in lysosomes [1]. As a group, neuronal ceroid lipofuscinosis (NCL) is the most common neurodegenerative disorder of childhood, but it also affects adults [2]. According to age of onset, various subtypes of NCL classified have been described (e.g. infantile-onset, late-infantile-onset, juvenile-onset and adult-onset). Most childhood subtypes share typical clinical course as progressive decline in cognitive and motor functions, progressive retinopathy leading to blindness, refractory seizures and eventually premature death, while dementia predominant in adult-onset types [2,3]. Despite similar clinical findings, NCL-associated proteins have different cellular functions and sub-cellular localization. Various types of NCL have been described according to mutations in NCL-associated proteins (CLN1–CLN14). With advances in genetics of NCL, 14 types of NCL have been described till date [4]. NCL type-11 was first described in 2014 in two young adult siblings. This was described as an adult-onset NCL [5]. There have been no further reports of NCL-11 in literature. We here

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present a 14-year old girl with genetically confirmed NCL-11 with onset 13 years of age. To the best of our knowledge this is the first juvenile onset type of NCL-11 and most probably the third case of NCL-11 worldwide.

2. Case report

A 14-year old girl, born to consanguineous couple presented with recurrent seizures for the past one year. The seizures were of generalized clonic type lasting for 5–10 min and followed by post-ictal drowsiness for half to one hour. The frequency was initially once in 2 months and gradually increased to 1–2 per month in the last few months on carbamazepine and clobazam. There was no history of myoclonic jerks, falls/imbalance while walking. There were no visual disturbances like palinopsia, recurrent headaches or decline in hand writing/school performance. She had an elder sister who had seizures from 8-year of age and died at the age of 16-years with recurrent seizures and dementia. She had cerebellar atrophy on neuroimaging; however genetic studies were not done. On examination of index child, neurological examination including fundus was within normal limits except for a mild wide-based gait. Her neuropsychological evaluation revealed that she had borderline intelligence with poor short-term memory and analytical capabilities.

Her electroencephalogram (EEG) showed generalised epileptiform discharges with a normal background activity (Fig. 1). Magnetic resonance imaging (MRI) brain showed diffuse vermian and cerebellar atrophy with hypoplasia (Fig. 2). She was put on levetiracetam and clobazam. Carbamazepine was tapered and her seizures got controlled. After her fundus examination had normal findings on multiple occasion, we try to do electroretinogram (ERG). Unfortunately, because of photosensitivity, she threw a generalized seizure while performing the ERG. We could not complete the study and parents did not consent for a repeat ERG testing. Because of lack of facilities for electron microscopy, skin EM could not be done. In view of gradually increasing frequency of seizures, MRI showing diffuse cerebellar (mainly vermian) atrophy; a positive family history and consanguinity, a possibility of progressive myoclonic epilepsy secondary to neurodegenerative disorder like NCL was thought of and blood sent for next generation sequencing. The reports revealed homozygous pathogenic mutation in the progranulin gene *(GRN)* in exon 9 (chr17:42428807G>A; p.Trp304Ter) thereby suggesting a diagnosis of NCL type-11 (OMIM#614706).

After confirmation of this pathogenic mutation in index case, we did Sanger sequencing of both parents and the younger sibling. All three are carriers (heterozygous mutation) of the *GRN* gene mutation (Fig. 3A). As heterozygous mutations in *GRN* gene known to cause frontotemporal dementia (FTD), we had sent both parents and the uncle of the child to the neurology department for evaluation of dementia. Currently they do not have any symptoms of dementia. Age of the father and mother is 45 & 41 years respectively. Uncle is 52-year old. One uncle died 2 years back at the age of 55-years due to myocardial infarction. The parents denied any history suggestive of dementia in their parents or elders/relatives (Fig. 3B).

3. Discussion

NCL-11 has been described in only two siblings so far and results from homozygous progranulin gene mutation [5]. While one had progressive retinopathy presenting with palinopsia, recurrent generalized seizures (4 years later), moderate ataxia and subtle cognitive dysfunction, the other presented with seizures and developed visual complains two years later. MRI showed selective and severe cerebellar atrophy which was progressive with age. Our case resembled the second presentation and may develop visual symptoms with retinal changes in future. EEG results in this condition shows generalized poly-spike wave discharges and, electroretinogram reveals severe attenuation of both rod and cone responses [5,6]. MRI shows isolated progressive cerebellar atrophy like in our case. Electron microscopic examination of a skin biopsy demonstrated numerous fingerprint profiles in membrane-bound structures in eccrine-secretory cells and in endothelium [6].

NCL-11 has been reported to result from homozygous *GRN* gene mutation [5,6]. However, after the initial report with two siblings in 2012, there have been no new reports of NCL-11 and *GRN* mutations. Our patient with homozygous mutation *GRN* gene further supports the fact that mutations in *GRN* gene causes NCL-11 and NCL-11 can present in adolescents.

The *GRN* gene is encoded for the progranulin, a secreted glycoprotein, that modulate many cellular processes includes inflammation, wound repair and lysosome function [7]. In 2006, Backers and colleagues had discovered first *GRN* gene mutation in patients with frontotemporal dementia after that clinical significance of progranulin became more evident [8]. Heterozygous *GRN* mutations leads to haploinsufficiency of progranulin, which known to cause frontotemporal lobar degeneration (FTLD) that presents in later life with behavioral and cognitive impairment (seizures are unusual; ataxia and retinal involvement are absent) [7,8]. While homozygous *GRN* mutations leads to complete progranulin deficiency, results in lysosomal storage disease, NCL-11 [6,7]. FTLD is a clinically heterogenous, and second most common cause of adult-onset dementia after Alzheimer's disease [7]. Despite of clinical diversities between FTD and NCL-11 patients, brain pathology showed some similarities in both disease as gliosis,

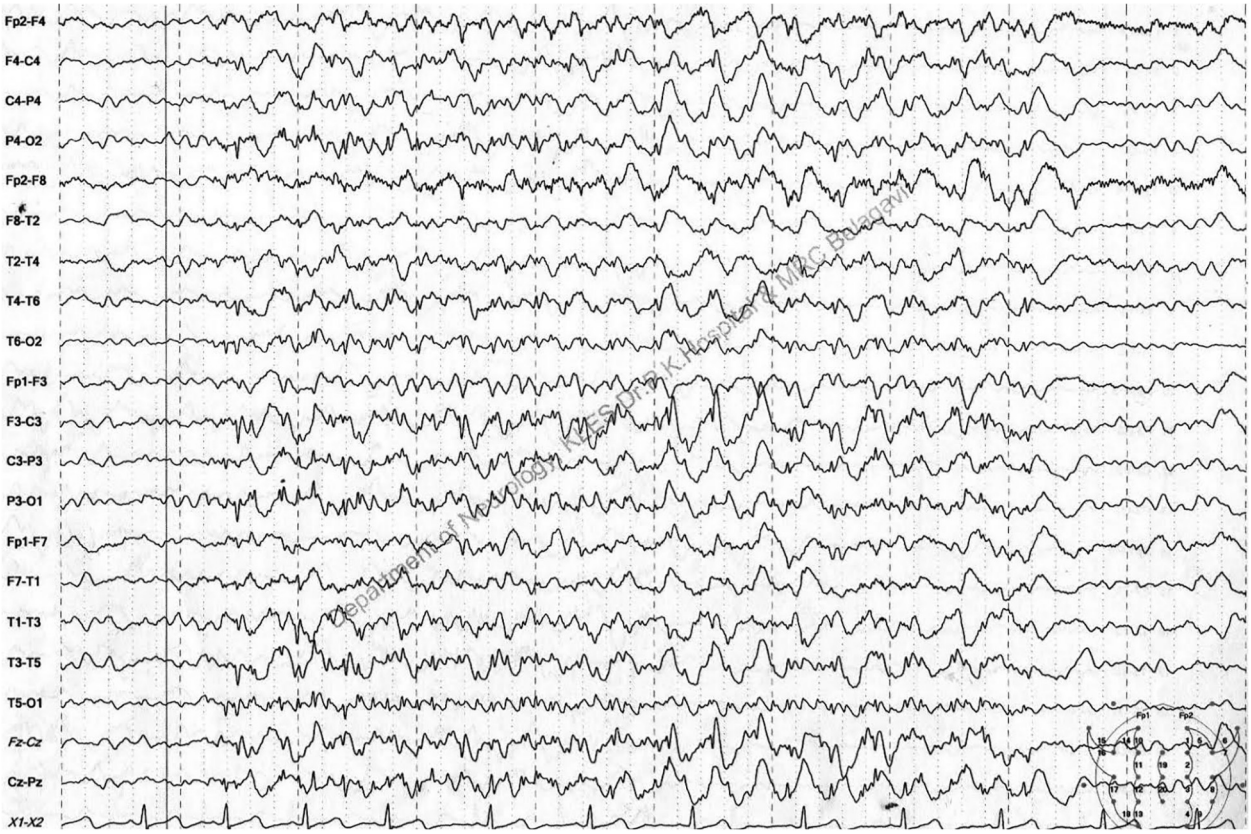

Fig. 1. Electroencephalogram showing generalized epileptiform discharges lasting for seven seconds with a normal background activity.

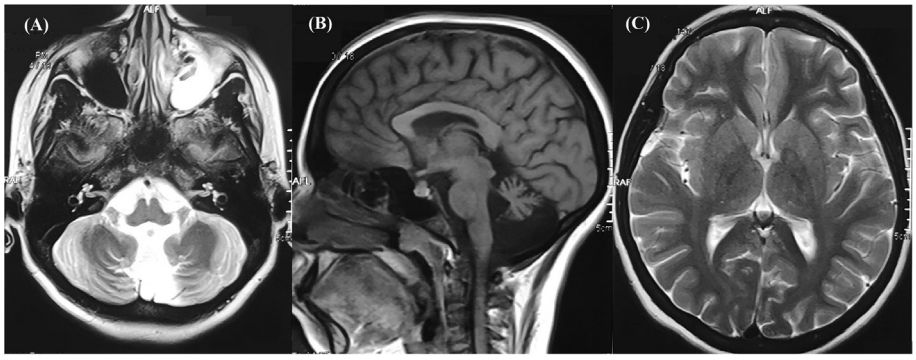

Fig. 2. A, B: T2W axial section of the brain at the level of cerebellum and T1W sagittal section of the brain respectively showing isolated cerebellar atrophy (mainly vermian) with hypoplasia. C: T2W axial section of the brain at the level of the basal ganglia showing normal cerebral cortex, basal ganglia and absence of periventricular white matter changes.

increased level of lysosomal proteins and lipofuscinosis found in both [9]. Based on the fact that both diseases associated with *GRN* mutations related progranulin deficiency, recently a therapeutic approach have been developed in mice model to increase progranulin level via progranulin gene therapy [10]. This study showed widespread reduction of lipofuscinosis and microgliosis after restoration of progranulin, which gives opportunities for possible treatment in future.

To conclude, NCL-11 resulting from homozygous *GRN* mutations can present in childhood with insidious onset seizures and isolated cerebellar atrophy.

Contributors

MK diagnosed and was involved in management of patients. He will act as guarantor of the study. MD collected the data and drafted the paper. VH read the neu-

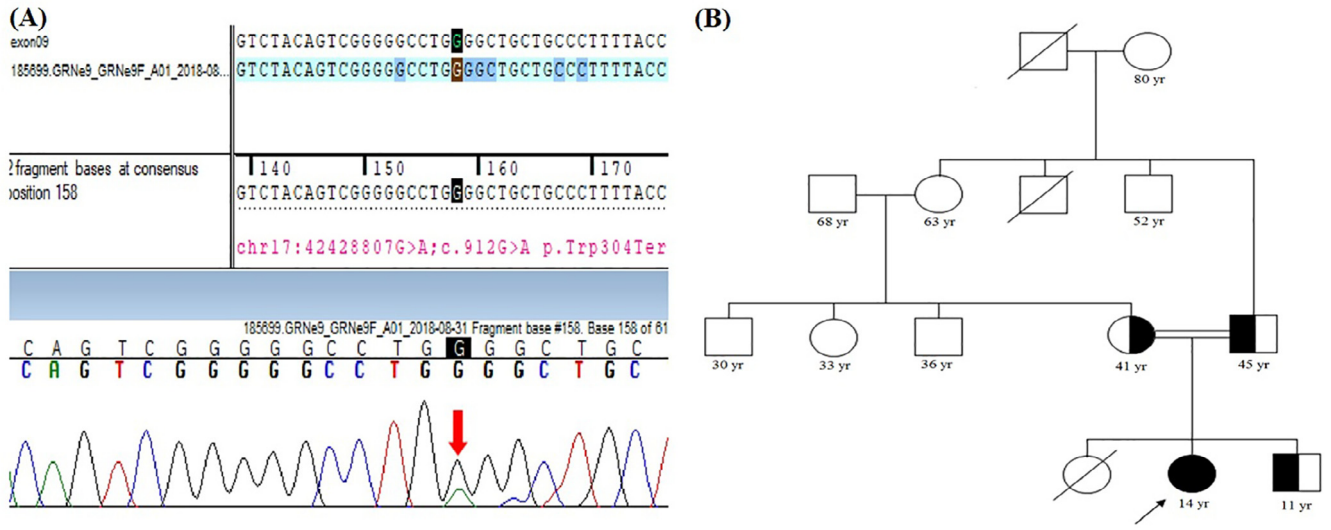

Fig. 3. A: Sequence chromatogram and alignment to the reference sequence showing the variation in exon 9 of *GRN* gene (chr17:42428807G>A; c.912G>A; p.Trp304Ter) detected in heterozygous condition in the younger sibling (Age-11 years) of the index patient. B: Three-generation pedigree.

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