JMD
https://doi.org/10.14802/jmd.20083 / J Mov Disord 2021;14(1):65-69
pISSN 2005-940X / eISSN 2093-4939

CASE REPORT

Sialidosis Type I without a Cherry Red Spot—Is There a Genetic Basis?

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ABSTRACT

Sialidosis is an inborn error of metabolism due to a defect in the *NEU1* gene and manifests as two phenotypes: mild type I and severe type II. The cherry red spot (CRS) is a characteristic feature in both types of sialidosis; reports of sialidosis without a CRS are rare. We report two cases of genetically confirmed sialidosis type I with a typical presentation of progressive cortical myoclonus and ataxia but without the CRS. A previously reported homozygous pathogenic variant p.Arg294Cys was detected in the first case, and a novel homozygous pathogenic variant p.Arg305Pro was detected in the second case. Additionally, we reviewed the literature describing cases with similar mutations to find a genetic basis for the absence of a CRS. Milder mutation of both alleles detected in both patients may be the reason for the absence of a CRS.

Key Words Ataxia; Cherry red spot; Mild mutation; Myoclonus; Sialidosis type I.

Sialidosis is an inborn error of metabolism secondary to the defects in the *NEU1* gene that leads to neuraminidase (NEU) deficiency. Two clinical phenotypes exist. Type I is known as 'cherry-red-spot myoclonus syndrome' and is milder, with an onset between adolescence and adulthood. Type I phenotype is manifested as visual disturbances, myoclonus, ataxia, mild or no cognitive abnormalities and no dysmorphic features. Type II is a severe congenital infantile or juvenile onset phenotype with dysmorphic facial and skeletal features, epilepsy, intellectual disability and organomegaly. The cherry red spot (CRS) is a characteristic feature in both phenotypes; however, a small percentage of cases may not have a CRS.[1-4] This report discusses two cases of genetically confirmed sialidosis type I without a CRS.

CASE REPORT

Case 1

A 33-year-old man presented with 14-year history of progressive shaking of the left upper limb (UL) followed by the right UL that 3 years later involved both lower limbs (LL). Shaking was predominantly action-induced, jerky, and led to occasional dropping of objects. The patient had difficulty walking and gait initiation along with an imbalance and falls. He also reported slurring of speech with no other bulbar symptoms. He had no significant family history. At presentation, the patient was independent, employed, and had comprehensible speech. A video was recorded after a written informed consent was obtained.

On examination, cognition was normal. Ophthalmological examination by a neuro-ophthalmologist was normal, including acuity, anterior segment and fundus examination. He had bilateral horizontal gaze-evoked nystagmus, mild cerebellar dysarthria, appendicular and axial incoordination, and ataxic gait. He had distal predominant, action-induced, multifocal myoclonus involving all four limbs with no sensory or auditory sensitivity. Upon standing, there were tremulous movements of both LL with an ataxic gait (Supplementary Video 1 in the online-only

Received: July 14, 2020 **Revised:** August 8, 2020 **Accepted:** August 21, 2020
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Data Supplement). The rest of the examination was normal. He was considered to be a case of progressive myoclonus ataxia (PMA) and was evaluated accordingly.

The routine blood investigations, ultrasound of the abdomen, and MRI of the brain were normal. Electrophysiological evaluation revealed giant somatosensory evoked potentials (SSEP) with N20−P25 amplitude of 14 μV (normal value < 10 μV), enhanced long loop reflexes, and frequent quasi-rhythmic bursts of < 50 ms duration in all four limbs according to the surface electromyography (EMG) suggesting the cortical nature of the myoclonus. Additionally, visually evoked potentials (VEP) showed bilaterally prolonged P100 latencies of 112 ms on the right eye and 114 ms on the left eye (normal value 106 ± 4 ms). However, electroencephalogram (EEG) and nerve conductivity study (NCS) were normal. Clinical exome sequencing revealed a previously reported pathogenic homozygous missense variant in exon 5 of the *NEU1* gene (chr6: g.31827960G>A; p.Arg294Cys; ENST 00000375631.4).[4,5] Based on the clinical and genetic data, the patient was diagnosed with sialidosis type I and was treated with clonazepam, sodium valproate, and levetiracetam. He had mild improvement in myoclonus, gait, and falls.

Case 2

A 14-year-old boy with a second-degree consanguineous parentage presented with one-year history of tremulousness in both ULs, which was postural, jerky, and affected his daily activities. He also had a mild imbalance while walking with difficulty negotiating narrow passages and had difficulty riding a bicycle. He had a history of decreased hearing in the left ear. There was no significant family history pertaining to his illness. The video was taken after a written informed consent was obtained.

On examination, the patient had mild deficits in executive function, verbal memory, and verbal fluency. Ophthalmological examination by a neuro-ophthalmologist was normal, including acuity, anterior segment, and fundus examination. There were hypermetric saccades, jerky pursuits, bilateral gaze-evoked nystagmus, and sensorineural hearing impairment in the left ear. There were subtle, distal predominant, postural and action-induced myoclonic jerks in ULs (Supplementary Video 2 in the online-only Data Supplement). Appendicular incoordination and wide-based and ataxic gait with impaired tandem was also noted (Supplementary Video 2 in the online-only Data Supplement). The rest of the neurological and other system examinations were normal. Based on these findings, PMA was suspected, and he was evaluated.

The routine investigations including plasma ammonia and plasma lactate, and ultrasound of the abdomen was performed and were normal. Pure tone audiometry revealed mild bilateral sensorineural hearing loss. Electrophysiological evaluation revealed giant SSEP with N20−P25 amplitude of 34 μV (normal value < 10 μV), enhanced long loop reflexes, and frequent quasi-rhythmic bursts of < 50 ms duration in all four limbs according to the surface EMG suggesting cortical nature of the myoclonus. Bilateral VEP had prolonged P100 latencies of 128 ms on the right eye and 131 ms on the left eye (normal value 106 ± 4 ms). EEG and NCS were normal. The clinical exome sequencing revealed a novel homozygous missense variant in exon 5 of the *NEU1* gene (chr6: g.31827926C>G; p.Arg305Pro; ENST 00000375631.4). This variant was classified as likely pathogenic according to the American College of Medical Genetics guidelines (PM2, PM5, PP2, and PP3).[2] The final diagnosis of sialidosis type I was made based on these observations.

DISCUSSION

The CRS is a characteristic feature of sialidosis, which is a lysosomal storage disorder caused by alpha-N-acetyl NEU deficiency secondary to *NEU1* gene mutations. In the present report, both cases had an onset of the symptoms in the second decade with cortical myoclonus followed by ataxia and without dysmorphism or organomegaly, i.e., a sialidosis type I presentation. However, contrary to the usual description of a cherry red spot-myoclonus syndrome, both patients lacked a CRS.[1] Interestingly, the patients did not have a CRS or visual disturbances; however, VEP was prolonged in both patients. To the best of our knowledge, this is the first report of sialidosis type I without a CRS from India.

More than 40 different mutations have been reported in the *NEU1* gene; most mutations are missense. Diverse clinical phenotypes result from the genotypic heterogeneity. Manifestations of the mutations of the *NEU1* gene vary from mild to severe. Genotype-phenotype correlation studies suggested that residual NEU activity is present in mild mutations; however, the activity is absent in severe mutations leading to type II phenotype.[6] To explain the phenotypic characteristics of two cases described in the present report (especially the absence of a CRS) based on their genotype, we analyzed the previously reported cases having either an identical amino acid substitution or a different amino acid substitution in the same locus (Table 1).

Our first case had a homozygous mutation of the *NEUI* gene resulting in the p.Arg294Cys amino acid substitution. This mutation has been previously described in two case reports, including a homozygous case and a compound heterozygous case. The case with homozygous p.Arg294Cys mutation had a phenotype similar to that observed in our study, i.e., progressive myoclonus and ataxia without a CRS and seizures.[4] However, unlike our case, there was cognitive impairment, reduced visual

Table 1. Previously reported sialidosis type I cases with genotypes similar to those in the present study

Study	Cases	Variant	Cherry red spot	VEP (P100 latency)	Vision
Present study	Case 1	c.880C>T; p.Arg294Cys c.880C>T; p.Arg294Cys	Absent	Prolonged	Normal
	Case 2	c.914G>C; p.Arg305Pro c.914G>C; p.Arg305Pro	Absent	Prolonged	Normal
Bou Ghannam et al.[4]	One	c.880C>T; p.Arg294Cys* c.880C>T; p.Arg294Cys*	Absent	NA	Affected
Ranganath et al.[5]	One	c.880C>T; p.Arg294Cys* c.1191delG; p.Arg397fs	Present	NA	Normal
Bonten et al.[6]	Two	c.878C>T; p.Arg294Ser* c.690T>A; p.Leu231His	Present	NA	Normal
		c.898C>T; p.Arg294Ser* c.654G>A; p.Gly218Ala	Present	NA	Affected
Canafoglia et al.[2]	Three	c.913C>T; pArg305Cys* c.679G>A; pGly227Arg	Absent	Normal	Affected
		c.913C>T; pArg305Cys* c.679G>A; pGly227Arg	Absent	Normal	Normal
		c.913C>T; pArg305Cys* c.679G>A; pGly227Arg	Absent	Normal	Normal

*variants identical or similar to the present study. NA: not available, VEP: visual evoked potentials.

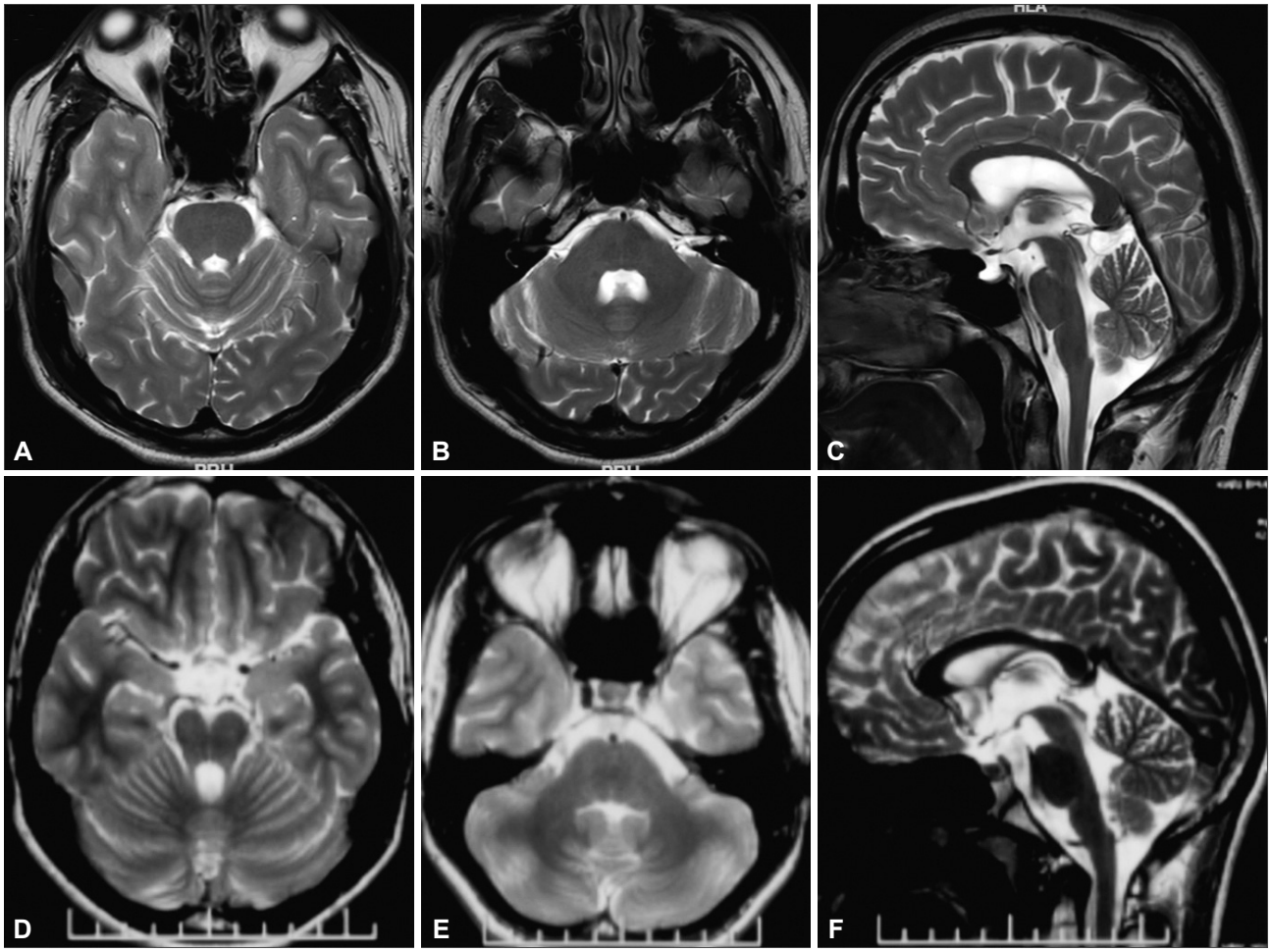

Figure 1. Brain MRI of two cases described in this report. Brain MRI of case 1 showing normal cerebellum and cerebellar peduncles (A-C). Brain MRI of case 2 showing atrophy of cerebellar vermis (D, F) and superior (D) and middle (E) cerebellar peduncle.

acuity, nyctalopia, latent squint, skew deviation, mild thickening in perifoveal macula on optical coherence tomography (OCT), and cerebellar atrophy according to MRI of the brain. Another case with compound heterozygous mutation of the *NEUI* gene had a p.Arg294Cys mutation in one allele and a more severe truncating frame shift mutation in the other allele resulting in a typical type I phenotype, i.e., progressive ataxia, myoclonus, and a CRS.[5] Two cases of sialidosis type I with a CRS were reported by Bonten et al.[6] to have a different amino acid substitution at the same locus (p.Arg294Ser). However, in both cases, there was an additional severe mutation of the other allele in compound heterozygous state. A review of previously reported genetically validated cases of sialidosis type I described 20 of 21 cases without a CRS as having a combination of 4 missense variants (p.Ser182Gly, p.Gly227Arg, p.R305C, and p.S67I).[7] Fourteen patients had homozygous p.Ser182Gly variant, 3 patients had homozygous p.Ser67Ile variant, 2 patients had compound-heterozygous p.Gly227Arg/p.Arg305Cys variants, and 1 patient had compound-heterozygous p.Ser182Gly/p.Gly227Arg variants.[2,3,7] Hence, it is possible that milder mutations of both alleles may lead to a type I phenotype without a CRS and a severe mutation of one of the alleles may lead to a type I phenotype with a CRS. The slow rate of progression and lower severity of the illness in our first case, who had a 14-year-long duration of the illness, supports the relatively benign nature of this mutation (p.Arg294Cys).

Our second case had a novel homozygous p.Arg305Pro amino acid substitution. A different amino acid substitution in the same locus (p.Arg305Cys) has been reported to result in a type I phenotype similar to the phenotype observed in our case, which was characterized by myoclonus, ataxia, no seizures, normal acuity, no CRS, and enhanced SSEP but with a later age at onset, normal VEP, and normal MRI of the brain. However, it was a compound heterozygous configuration with a different missense mutation (p.Gly227Arg) (Table 1).[2] A CRS may sometimes appear later in the course of the illness when the deposition of sialylated glycoproteins is increased[8]; since our second case was examined within a year of the onset of the illness, a prolonged follow up is required. OCT and autoflourescence examination of the fundus are more sensitive and can demonstrate retinal changes even when the fundus examination is otherwise normal.[9] Additionally, a CRS may become less conspicuous with disease progression because ganglion cells die leading to the loss of distinction between the fovea and the surrounding region.[10] Environmental factors, diet, and genetic factors in addition to NEU mutations may play a role in the phenotypic heterogeneity.[6]

In conclusion, although the CRS has been described as a characteristic finding in sialidosis, it may be absent in cases of sialidosis type I with milder mutations of both alleles. Therefore, the absence of a CRS should not preclude a diagnosis of sialidosis in patients who present with PMA syndrome.

Supplementary Video Legends

Video 1. Clinical examination of case 1: Video showing mild dysarthria, postural jerky tremor, distal and action predominant cortical myoclonus, incoordination during finger-to-nose test and knee-heel-shin test, and ataxic gait.

Video 2. Clinical examination of case 2: Video showing postural jerky tremor, distal and action predominant cortical myoclonus, incoordination during finger-to-nose test, ataxic gait, and impaired tandem gait.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.20083.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgments

None

Author Contributions

Conceptualization: Koti Neeraja, Vikram Venkappayya Holla, Pramod Kumar Pal. Data curation: Vikram Venkappayya Holla, Koti Neeraja, Shweta Prasad, Bharath Kumar Surisetti, Kempaiah Rakesh. Supervision: Nitish Kamble, Ravi Yadav, Pramod Kumar Pal. Writing—original draft: Koti Neeraja, Vikram Venkappayya Holla, Kempaiah Rakesh. Writing—review & editing: Shweta Prasad, Bharath Kumar Surisetti, Nitish Kamble, Ravi Yadav, Pramod Kumar Pal.

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