CASE REPORT

Syndrome of X linked intellectual disability, epilepsy, progressive brain atrophy and large head associated with *SLC9A6* mutation

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Accepted 9 December 2017

SUMMARY

SLC9A6 gene encodes for a sodium/hydrogen exchanger-6 protein mainly involved in endosomal trafficking and maintaining intraluminal pH. Loss of function mutations in *SLC9A6* gene in children has been associated with Christianson syndrome and autism spectrum disorder. We describe a 3-year-old boy with intellectual disability, infantile-onset drug-refractory epilepsy, progressive brain atrophy and large head with a novel missense hemizygous mutation in exon 16 of the *SLC9A6* gene on chromosome X. Presence of large head, early developmental regression and progressive cerebral atrophy expand the phenotypic spectrum of *SLC9A6* mutations. Our case also highlights the importance of genetic testing in children with unexplained intellectual disability, epilepsy and neurodevelopmental impairments.

BACKGROUND

Mutations in the *SLC9A6* gene-encoding sodium/hydrogen exchanger-6 (NHE-6) protein have been associated with Christianson syndrome characterised by X linked intellectual disability, epilepsy, ophthalmoplegia, microcephaly, craniofacial dysmorphism and progressive cerebellar atrophy.¹ Apart from Christianson syndrome, mutations in *SLC9A6* gene have also been recently implicated as one of the plausible mechanisms in the complex pathogenesis of autism spectrum disorder.² We describe a 3-year-old boy with intellectual disability, infantile-onset drug-refractory epilepsy, progressive brain atrophy and large head with a novel missense hemizygous mutation in exon 16 of the *SLC9A6* gene.

CASE PRESENTATION

A 3-year-old boy, first born to non-consanguineous parents, presented with global developmental delay, recurrent seizures and large head noticed since early infancy. His developmental age at 3 years was between 6 and 7 months in all the sectors. He had focal (right-sided) and generalised tonic-clonic seizures at the onset of epilepsy and later developed epileptic spasms occurring at a frequency of 10–12 episodes/day. He was born at term by caesarean section, weighed 3.4 kg at birth with occipitofrontal circumference of 36 cm. Perinatal period was uneventful. Family history was unremarkable.

On examination, his weight was 10 kg (between –2 and –3 Z score), length 87 cm (between –2 and

–3 Z score) and head circumference 52 cm (+2 Z score). Parent's head circumference was normal (mother 55 cm and father 55.5 cm). He had elongated forehead, depressed nasal bridge, long philtrum, dolichocephalic head (figure 1A), single large mongoloid spot over the buttocks, normal fundi, central hypotonia, brisk muscle stretch reflexes and bilateral Babinski's sign. The rest of the systemic examination was not contributory. A clinical diagnosis of intellectual disability with large head and epilepsy secondary to either a structural, metabolic or genetic cause was considered.

INVESTIGATIONS/DIFFERENTIAL DIAGNOSIS

Laboratory investigations showed normal pH, serum ammonia and arterial lactate levels, tandem mass spectrometry/gas chromatography-mass spectrometry, cerebrospinal fluid (CSF) neurotransmitter levels and skeletal survey. Sequential MRI of the brain done at 9 months, 11 months and 3 years of age showed progressive, diffuse cerebral and cerebellar atrophy (figure 1B,C). Electroencephalography showed right hemispheric slowing with frequent bilateral frontotemporal interictal discharges. In view of progressive brain atrophy, neurodegenerative disorders such as GM2 gangliosidosis, neuronal ceroid lipofuscinosis, atypical Rett and glucose transporter type 1 deficiency syndrome were considered. Plasma total hexosaminidase (A+B) enzyme was 3.32 nmol/hour/mL (normal 0.66–5.0) and hexosaminidase A was 37.5 nmol/hour/mL (normal 20–96.5). Genetic analysis for neuronal ceroid lipofuscinosis by next-generation sequencing was negative. CSF glycine was 62.23 mmol/L (5–40 mmol/L) and CSF glucose was 62 mg%. A next-generation sequencing to identify variants in the targeted genes relevant to clinical indication was performed. Clinically relevant mutations were annotated using published variants in literature and a set of variant databases. Only non-synonymous and splice site variants were used for clinical interpretation. Silent variations that do not result in any change in amino acid were not used. A hemizygous missense variation (chrX:135122338; G>A; c.1675G>A) that resulted in the amino acid substitution of lysine for glutamic acid at codon 559 (p.E559K; ENST00000370701) was detected in exon 16 of *SLC9A6* gene in index

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To cite: Padmanabha H, Saini AG, Sahu JK, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-222050

Figure 1 (A) Clinical photograph of the patient showing subtle facial dysmorphism: elongated face, dolichocephalic head, deep sunken eyes, long philtrum and a depressed nasal bridge. MRI (B) T1 and (C) T2-weighted axial sections at 3 years of age showing diffuse cerebral atrophy.

patient and was further validated using Sanger sequencing. No additional pathogenic variants were detected in the index child. The mother was heterozygous for the same mutation and was asymptomatic. She is a graduate and working as a school teacher. She did not have any dysmorphism, epilepsy or behavioural problems. The p.E559K variant was also detected by Sanger sequencing in the mother's sister as shown in the family pedigree (figure 2). However, both her daughters remain unaffected, suggesting a probable X linked recessive inheritance. Chorionic villous sampling done for the fetus in second pregnancy revealed the same mutation and parents opted for medical termination of pregnancy.

TREATMENT

He was administered antiepileptic drugs (valproate 50 mg/kg/day, levetiracetam 60 mg/kg/day, clobazam 0.5 mg/kg/day), biotin (20 mg/day) and pyridoxine (15 mg/kg/day).

OUTCOME AND FOLLOW-UP

At last follow-up, at 6 years of age, his developmental age is between 8 and 10 months and head circumference is 55 cm (between +2 and 3 Z score). He is non-verbal, has feeding difficulties and persists to have polymorphic seizures. Both the parents remain asymptomatic.

DISCUSSION

SLC9A6 gene encodes an NHE-6 protein, which is present in the membranes of intracellular organelles like mitochondria and endosomes. The NHE-6 proteins are mainly involved in early recycling of endosomal membranes, maintaining

luminal pH and are important for growth of dendritic spines and synaptic arborisation.³ Thus, loss of function in NHE-6 affects synaptic development and long-term potentiation, which is essential for learning and memory processing.⁴ Impairments in these functions possibly result in intellectual disability and epilepsy. Understandably, *SLC9A6* has been implicated as one of the six major causes of X linked intellectual disability with diverse phenotypes.⁵

Extensive tau deposits in neuronal and glial tissue, and abnormal interaction of *SLC9A6* with vesicular transport can be postulated to cause neuroregression and other degenerative processes such as retinitis pigmentosa.^{6,7} The onset of neuroregression has been commonly seen after the first decade of life.⁸ The early (onset at 2 years) developmental regression seen in our patient may be attributed to one or more of these mechanisms and epileptic encephalopathy. Similar mechanisms may also have caused progressive, diffuse cerebral atrophy on neuroimaging although mutations in *SLC9A6* gene have been characteristically associated with progressive cerebellar atrophy in the majority (60%) of patients.⁹

The characteristic craniofacial features described with *SLC9A6* mutations include a long narrow face, a prominent straight nose, square-shaped prognathic jaw, large ears, deep sunken eyes and bushy eyebrows.¹ The index child also had some of these dysmorphic features pointing to a possible genetic aetiology. The unique feature in the index case is the presence of a large head size since birth. Mutations in *SLC9A6* gene, including the phenotype of Christianson syndrome, are reported to be associated with postnatal microcephaly in the majority (92%) followed by a normal head circumference in the rest.¹⁰ Hence, association of large head (relative macrocephaly in comparison to the short stature) with *SLC9A6* possibly describes a new phenotype of this genetic disorder and description of more cases will further expand our knowledge of the spectrum of *SLC9A6* mutation-associated genetic syndromes.

CONCLUSION

SLC9A6 gene mutations may be associated with wider clinical phenotypes than are currently known. Our case highlights a novel phenotype of intellectual disability, infantile-onset drug-refractory epilepsy, progressive brain atrophy and macrocephaly-associated *SLC9A6* mutations.

Learning points

- ▶ A novel phenotype of intellectual disability, infantile-onset drug-refractory epilepsy, progressive brain atrophy and large head is associated with *SLC9A6* mutations.
- ▶ Genetic testing in children with unexplained intellectual disability, epilepsy and neurodevelopmental impairments is important.
- ▶ Female carriers with *SLC9A6* mutations may remain asymptomatic or have mild to moderate intellectual disability, behavioural issues and various psychiatric illnesses.

Contributors HP, AGS: patient management, draft of manuscript and review of literature. JKS: patient management and final review of manuscript for intellectual content. PS: clinician-in charge, plan of the study and critical review of manuscript for intellectual content.

Competing interests None declared.

Patient consent Guardian consent obtained.

Figure 2 Pedigree of the family.

Provenance and peer review Not commissioned; externally peer reviewed.

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