


CASE REPORT

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Infantile Sandhoff disease with ventricular septal defect: a case report

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Abstract

Background: Infantile Sandhoff disease is a rare inherited disorder that progressively destroys nerve cells in the brain and spinal cord, and is classified under lysosomal storage disorder. It is an autosomal recessive disorder of sphingolipid metabolism that results from deficiency of the lysosomal enzymes β -hexosaminidase A and B. The resultant accumulation of GM2 ganglioside within both gray matter nuclei and myelin sheaths of the white matter results in eventual severe neuronal dysfunction and neurodegeneration.

Case presentation: We evaluated a 3.5-year-old Comorian girl from the United Arab Emirates who presented with repeated chest infections with heart failure due to ventricular septal defect, neuroregression, recurrent seizures, and cherry-red spots over macula. She had macrocephaly, axial hypotonia, hyperacusis, and gastroesophageal reflux. Organomegaly was absent. Brain magnetic resonance imaging, metabolic tests, and genetic mutations confirmed the diagnosis. Despite multidisciplinary therapy, the girl succumbed to her illness.

Conclusion: Though early cardiac involvement can be seen with novel mutations, it is extremely rare to find association of ventricular septal defect in infantile Sandhoff disease. Neuroregression typically starts around 6 months of age. We report this case because of the unusual association of a congenital heart disease with underlying infantile Sandhoff disease and symptomatic heart failure in the first month of life with eventual fatal outcome.

Keywords: Infantile Sandhoff disease, Ventricular septal defect, Hexosaminidase, Neuroregression, Cherry-red spots, Hypotonia

Background

Lysosomal storage disorders (LSDs) are a specific group of inborn errors of metabolism including more than 50 different diseases caused by a structural defect or deficiency of lysosomal enzymes [1]. GM2 gangliosidosis is one group of LSD that is classified into three types: Sandhoff disease (SD), Tay–Sachs, and GM2 activator deficiency (GM2A-AB variant) [2]. SD is a rare autosomal recessive neurodegenerative disorder prevalent 1 in 384,000 live births, related to a genetic deficiency of

the enzyme β -hexosaminidase (HEX) [1]. There are two active forms of this enzyme— β -HEX A, composed of one α and one β subunit ($\alpha\beta$), and β -HEX B, which contains two β subunits ($\beta\beta$). In SD, there is a mutation in HEX B gene that encodes the α subunit, thereby leading to β -HEX enzyme deficiency [2]. Tay–Sachs disease, SD, and GM2AP deficiency are caused by biallelic pathogenic variants of human HEXA, HEXB, and GM2AP gene in respective order [3].

Gangliosides have been found within the gray matter nuclei and myelin sheaths of the white matter [4]. When GM2 gangliosides accumulate within lysosomes of cortical neurons, distension of neuronal cell bodies with displacement of nucleus occurs, which leads to cellular enlargement and severe neurodegeneration [4–9]. There

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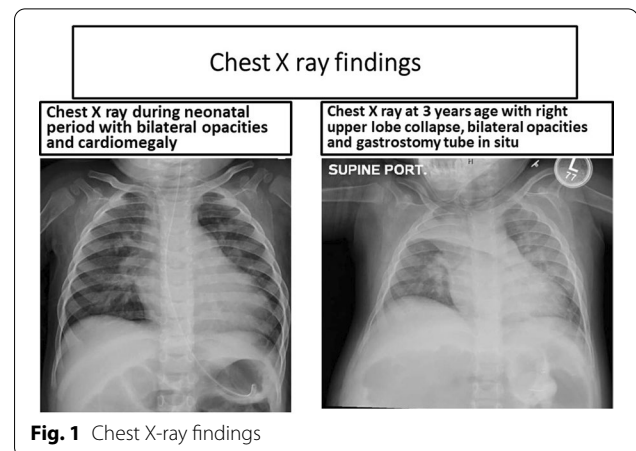
is evidence of demyelination as well as delayed myelination, which can be attributed to gray matter disease [10–12]. Autopsy findings are suggestive of lipid storage and edema formation in white matter [13].

Described by Warren Tay in 1881, the clinical manifestation can be divided into three forms based on age group: infantile, juvenile, and adult [14]. Infantile SD presents with truncal hypotonia, muscle weakness, hyperacusis, developmental delay and regression, seizure, and cherry-red spots on ophthalmologic examination around 6 months of age [15]. Hepatosplenomegaly, coarse facies, and bone abnormality are seen less often than Tay–Sachs disease [14]. Death occurs by 3 years of age owing to intractable seizure and aspiration pneumonia. Though late cardiac involvement is reported with cardiomegaly and heart murmur in SD, association of ventricular septal defect has not been reported in literature [16]. This rare case is reported for the purpose of acquaintance with clinical symptomatology, recognizing unusual association of congenital cardiac disease, identifying other comorbidities, and interpreting abnormal neuroradiology.

Case presentation

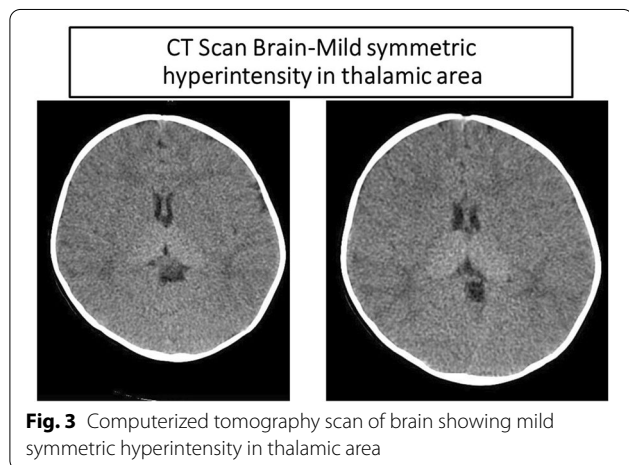
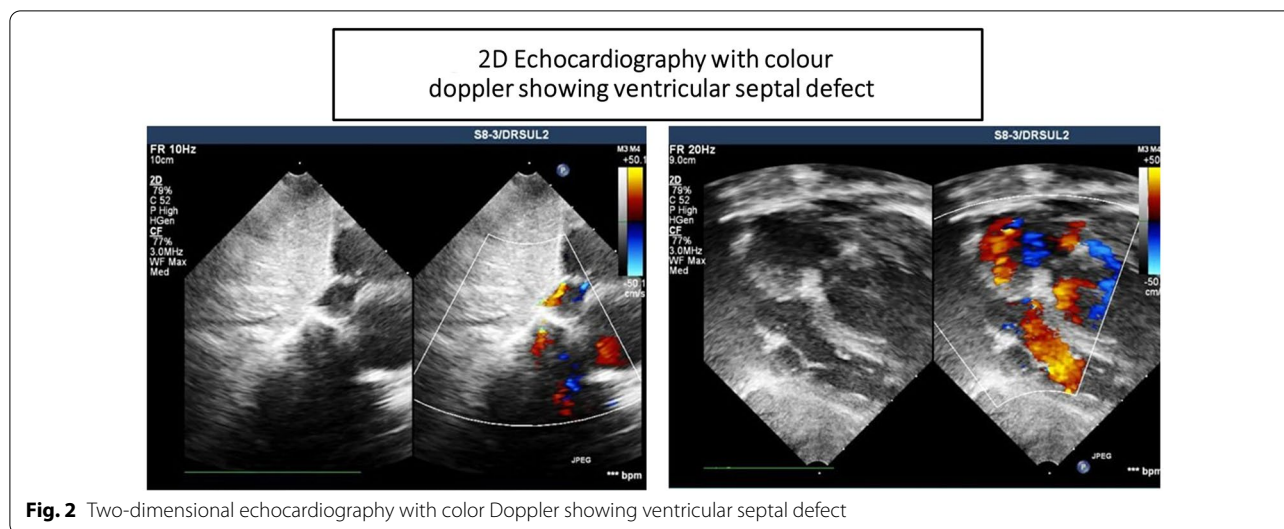
We evaluated a Comorian girl aged 3 years 6 months with neuroregression and seizures. The child was third born to second-degree consanguineous parents by lower-segment cesarean section due to cephalopelvic disproportion. Birth weight was 3.1 kg with uneventful perinatal history. There was maternal history of normal healthy live birth in the first pregnancy and spontaneous miscarriages in second and fourth pregnancies in early trimesters. The fourth pregnancy was associated with Down syndrome. The mother was given antenatal progesterone for excess bleeding in the first trimester.

From 2 weeks of age, she presented with lethargy, sweating, and breathlessness on feeding. Later on, she presented with recurrent episodes of aspirations with severe lower respiratory infections. Cardiac examination revealed a holosystolic murmur suggestive of ventricular septal defect (VSD). Chest X-ray revealed cardiomegaly with features suggestive of pneumonia (Fig. 1). Echocardiography (ECHO) showed moderate VSD (6–7 cm subaortic perimembranous VSD), dilated left atrium and left ventricle, trivial aortic regurgitation with aortic cusp collapse, dilated pulmonary artery system with flow acceleration across pulmonary valve, and half-systemic pulmonary artery pressure with normal left ventricular systolic function (Fig. 2). There was no pericardial effusion or right ventricular outflow tract obstruction. She was managed medically with decongestive medications and antibiotics for lower respiratory infections. She was noted to have laryngomalacia. At 3 months of age, decreased motor movements were noted. She was



gaining weight till 5 months of age, after which there was flattening of the growth curve and failure to thrive. At 6 months, she had developmental arrest followed by progressive neuroregression. She also had severe startle response since 8 months of age. Then, she started having generalized recurrent seizures from 9 months onward. The epileptic episodes were mostly focal with secondary generalization, with the most severe event reported as having frequency of ten seizure episodes within 2 hours time period despite anticonvulsant therapy. She had also macrocephaly with coarse facial features, persistent laryngomalacia, and hyperacusis. There was no muscle atrophy. Central hypotonia, peripheral hypertonia, and a positive Babinski reflex were elicited. Organomegaly was absent. Ophthalmological examination showed bilateral macular cherry-red spots and an inability to fixate the eyes. At 12 months, she developed gastroesophageal reflux disease (GERD) as well as reactive airway disease. Gastrostomy tube feeding was also commenced. She had frequent episodes of hospitalizations due to repeated aspiration pneumonia, reactive airway diseases, and other central nervous system complications.

History and physical examinations pointed toward the diagnosis of GM2 gangliosidosis (Tay–Sachs disease, SD, AB variant). In view of cherry-red spots and coarse facies, GM1 gangliosidosis was also considered. No significant abnormality was noted in complete blood count, electrolytes, or renal and liver function tests. Ultrasonography of abdomen did not reveal any hydronephrosis or other anatomic abnormalities. Computerized tomography scan of brain without contrast was suggestive of mild bilateral symmetric hyperdensity of thalami (Fig. 3). Electroencephalogram (EEG) showed slowing of delta frequencies associated with drowsiness. Video-fluoroscopic assessment for swallowing function was suggestive of aspiration on both fluoroscopic runs. Magnetic



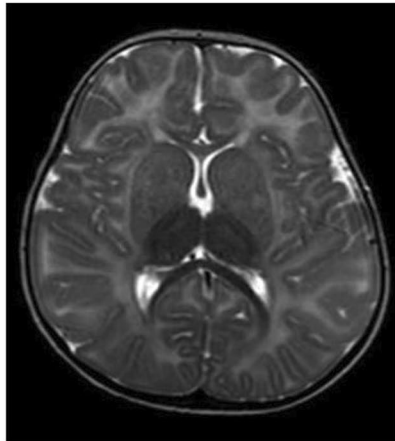
resonance imaging (MRI) of brain revealed extensive high signal within the supratentorial white matter involving subcortical and deep white matter structures. There was evidence of T1-increased signal in the thalamus and a relatively large head shape. Bilaterally, the thalami demonstrated symmetric reduction of T2 signal and increase in the T1-weighted signal. There was marked delay in myelination as demonstrated on T1-weighted imaging. The corpus callosum was markedly thinned in its anterior body and genu. There was mild hypoplasia of the posterior arch of the C1 vertebra causing minimal narrowing at the upper cervical spinal canal (Fig. 4).

Magnetic resonance spectroscopy (MRS) trace did not reveal high creatinine or *N*-acetyl aspartate (NAA) peaks. No significant lactate level was demonstrated (Fig. 5).

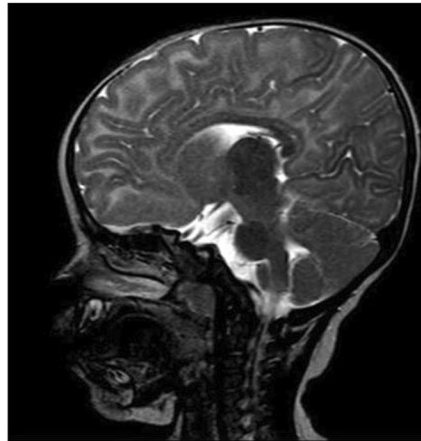
Metabolic workup revealed a serum finding of trace-to-absent total serum HEX A and HEX B (0.0 nmol/min/ml; reference value > 20 nmol/min/ml) explaining the deficiency of the β subunit of HEX and consequent deficiency of HEX B. The serum HEX A percentage was 100% (reference value 20–90%). This biochemical findings of low total HEX and deficient HEX B activities, with high percentage of HEX A/total HEX activity suggested the diagnosis of SD. Oligosaccharide urine screen was positive in the urine sample, and genetic testing confirmed the diagnosis of SD with homozygous deletion c.(445+1_512-1)_(669+1_1170) in the HEXB gene. The parents were advised to consent to genetic analysis, but they refused.

The patient was maintained on decongestive therapy (captopril, frusemide, spironolactone, and digoxin) and antiepileptics (levetiracetam and phenobarbitone). Fundoplication was done owing to her symptomatic GERD during infancy, and she was started on regular esomeprazole and domperidone, after which she was fed through gastrostomy tube. Fluticasone, ipratropium bromide and salbutamol nebulizations were continued in view of reactive airway disease. Iron supplementation was started in view of anemia. The clinical course is complicated with recurrent aspiration pneumonia warranting frequent hospital admissions. She also underwent multiple bronchoscopies. At 3 years of age, she had adenoviral

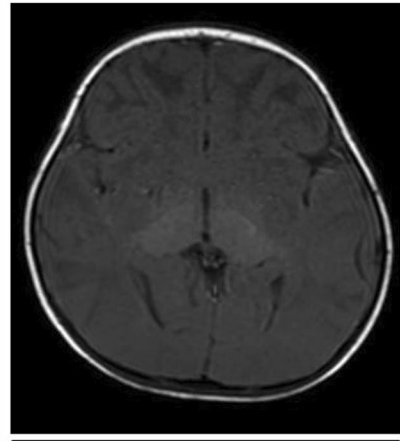
MRI Brain revealing extensive high signal within the supratentorial white matter involving subcortical and deep white matter structures and thinned out corpus callosum



Axial T2WI at the thalamic level demonstrating bilateral diffusely hypointense thalami and delayed myelination



Coronal T2WI at the thalamic level demonstrating diffusely hypointense thalami



Axial T1WI demonstrating diffusely hyperintense thalami

Fig. 4 Magnetic resonance imaging of brain revealing extensive high signal within the supratentorial white matter involving subcortical and deep white matter structures and thinned-out corpus callosum

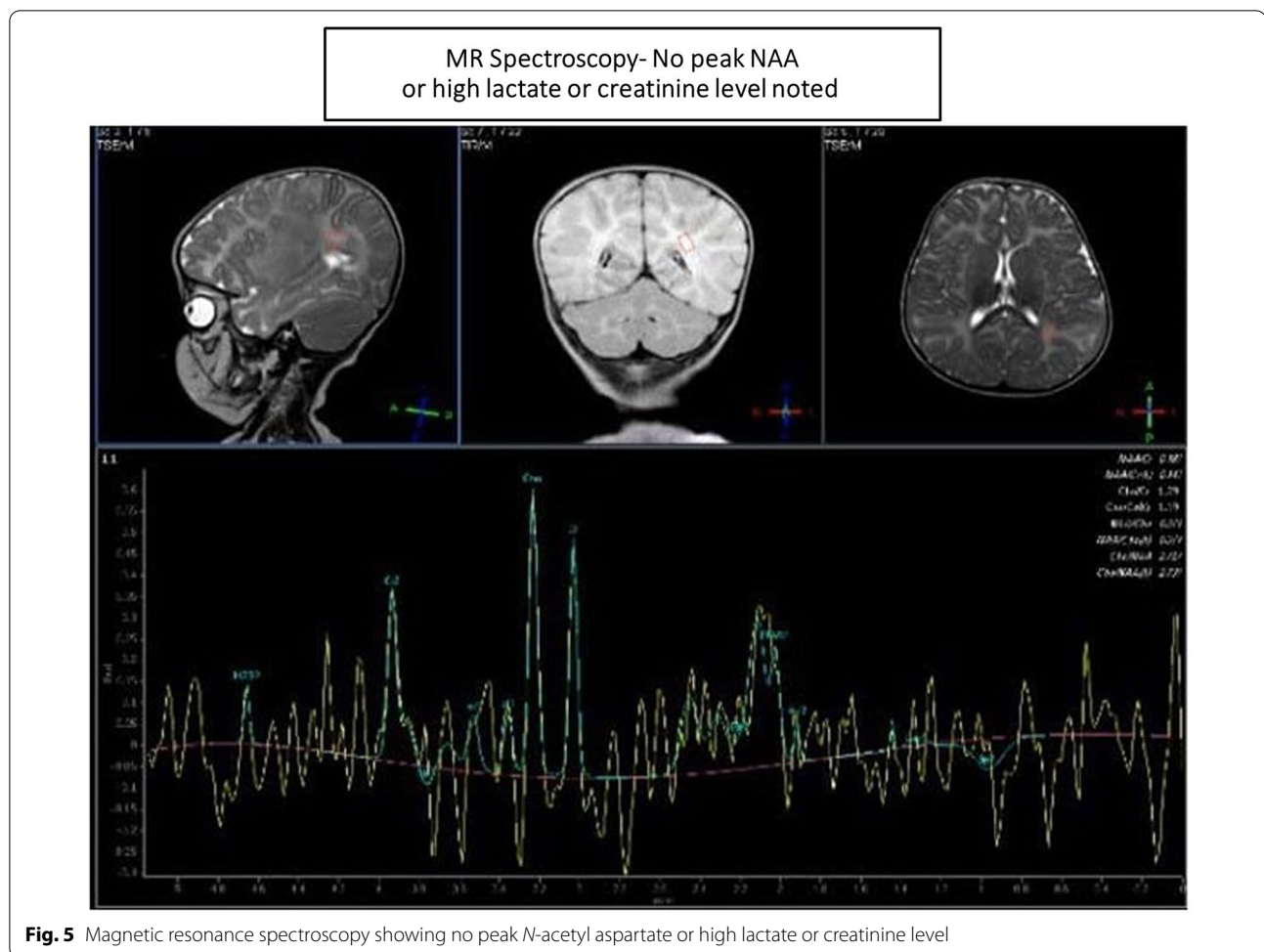
infection on respiratory BioFire assay and then developed *Pseudomonas* pneumonia. Despite treatment with piperacillin–tazobactam, ciprofloxacin, tobramycin, and clindamycin antibiotics, her cardiorespiratory status worsened and she became ventilator dependent. Tracheostomy was performed at 3 years of age. However, despite the multimodality care with cardiology, neurology, pulmonology, physiotherapy, and nutritional and ventilatory support, she died at 3 and half years of age (Fig. 6).

Discussion and conclusions

SD is an autosomal recessive lysosomal storage disorder on chromosome 5q13 and was first described by Konrad Sandhoff in 1968. It is due to hexosaminidase A and B enzyme deficiency (due to an abnormal β subunit) leading to accumulation of glycosphingolipids in neuronal cells and subsequent neurodegeneration [14]. The juvenile form of SD is present between 2 and 10 years of age with dysarthria, ataxia, mental deterioration, and seizures. Organomegaly and cherry-red spots are uncommon. The adult form of SD is characterized by movement disorder, pyramidal and extrapyramidal signs and symptoms of lower motor neuron disease, and supranuclear ophthalmoplegia [14]. Progressive systemic accumulation

of sphingolipids leads to macrocephaly, cherry-red spots in the eye, skeletal dysostosis, and organomegaly [17].

In a study of infantile-onset Sandhoff disease in 2018 in Iran, involving 25 patients with the condition, the most common and earliest clinical manifestations were motor and cognitive milestones delay and regression [2]. Cherry-red spots are a characteristic ocular and physical sign of infantile SD and can be used for early detection in patients who are suspected to have this disease. Organomegaly was detected in only two patients, and some associations between diffuse Mongolian spots and SD were found to be significant [2]. Accumulation of calcium associated with collection of GM2 ganglioside leads to gliosis and loss of myelin and axon in cortical neurons, giving rise to some of the earliest findings on T2-weighted images of brain MRI, including bilateral thalamic hypodensity and hypomyelination, that are characteristic of brain involvement in the infantile SD disease, which were detected in the same study [7, 18]. An increase in a specific marker *N*-acetylhexosamine at 2.07 ppm in white matter and thalamus on proton MR spectroscopy of patients with SD was also reported, in addition to the mentioned finding [15, 19]. Diagnosis is confirmed by enzymatic assays revealing a deficiency of both lysosomal hydrolase β -HEX A and β -HEX



B. Decreased levels of HEX A and HEX B are seen in patients with SD but solitarily decreased levels of HEX A are seen in Tay–Sachs disease [19]. Genetic study is important to make definitive diagnosis and to help family planning and prenatal diagnosis in affected families [2]. As there is a high rate of association with consanguineous marriages and SD seen in several studies, it is very important that all couples be advised to undergo premarital genetic testing and counseling for any carrier genes.

Though cardiac involvement has been reported in an 18-month-old boy alongside the classical neurological features, the child exhibited severe mitral regurgitation secondary to mitral valve prolapse and mild aortic regurgitation from aortic valve prolapse. He also had asymmetric hypertrophy of the interventricular septum without left ventricular outflow tract obstruction [16]. Similarly, another case report describes a 14-month-old

female baby who exhibited mitral regurgitation and cardiomegaly at the age of 2 months and dilation of the left atrium and left ventricle at the age of 6 months with SD [20]. However, congenital heart disease such as ventricular septal defect has not yet been reported in infantile SD. The association of VSD with Sandhoff disease is likely coincidental, and there is no pathophysiological mechanism to explain this association.

The disease progresses rapidly, with deaths occurring by 3–5 years of age. Case fatality in the infantile form typically occurs before the age of 4 owing to extensive and severe central nervous deterioration [21]. For the treatment of SD, studies are still being conducted worldwide, and a definitive treatment other than supportive measures has not yet been recommended. One ongoing study in Tehran, Iran is showing efficacy of miglustat therapy

Case Time line	
Age	Events
2 weeks	Breathlessness, sweating on feeding, fatigue
4 weeks	Lower respiratory tract infection-treated with antibiotics Diagnosis of ventricular septal defect-treated medically with antifailure therapy, laryngomalacia
3 months	Decreased psychomotor activity
5 months	Growth curve flattening, failure to thrive, pneumonia
6 months	Developmental arrest, neuroregression started
7 months	Decreased ability of eyes to follow moving objects (visual inattention), episode of lower chest infection
8 months	Severe Startle response, hyperacusis
9 months	Recurrent seizures despite antiseizure medications, macrocephaly, EEG done, Ophthalmoscopy- cherry-red spots, aspiration pneumonia
12 months	Significant axial hypotonia, peripheral hypertonia, loss of developmental milestones, Gastroesophageal reflux disease, reactive airway disease Fundoplication done for GERD, Gastrostomy tube feeding
14 months	Repeated lower respiratory infections every one to one half month intervals
3 year	Acute respiratory distress syndrome, Pseudomonas pneumonia, Tracheostomy due to ventilator dependency
3 year 6 months	Death due to cardio respiratory failure

Fig. 6 Case timeline

in SD, but miglustat is not yet an approved drug for this condition [22].

In conclusion, infantile SD is an important differential diagnosis for each child presenting with neurologic symptoms such as developmental delay, neuroregression, and cherry-red spots on ophthalmic examination. Organomegaly is not a frequent clinical finding in infantile SD. There is genetic heterogeneity among patients with SD. Early cardiac involvement is rare. We report this case because of its rare association with acyanotic congenital heart disease and to emphasize the importance of proper genetic counseling.

Abbreviations

LSDs: Lysosomal storage disorders; SD: Sandhoff disease; HEX: Hexosaminidase; VSD: Ventricular septal defect; ECHO: Echocardiography; EEG: Electroencephalogram; GERD: Gastroesophageal reflux disease; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; NAA: N-acetyl aspartate.

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Author contributions

JS, LB, NA, and SK designed the study, collected the patient data, and coordinated the research. FM, SJ, and SK wrote the manuscript, coordinated the research, and analyzed the data. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of RAK Medical and Health Sciences University ref. no. RAKMHSU-REC-051-2020/21 UG-M.

Consent for publication

Written informed consent was obtained from the patient's legal guardian(s) for publication of this case report and any accompanying images in both English and Arabic. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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