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Case Report Open Access

Sengers Syndrome: A Rare Cause of HOCM

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Abstract

Sengers syndrome is a rare disorder that causes congenital cataract, hypertrophic cardiomyopathy (HOCM), skeletal myopathy and lactic acidosis. Hypertrophic cardiomyopathy is usually fatal in infancy. It is an autosomal recessive mitochondrial depletion disorder resulting from the mutation of acylglycerol kinase (*AGK*) gene. This nuclear gene is responsible for the maintenance of mitochondrial DNA (mDNA).

We report a 4 month old boy who had severe lactic acidosis at birth and progressive congenital cataract. Cataract and failure to thrive were missed on his primary examination until he presented with a squint and subsequently with heart failure secondary to severe hypertrophic cardiomyopathy. His genetic testing revealed a novel putative homozygous splicing mutation of *AGK* gene leading to the diagnosis of Sengers syndrome.

Uncertainty about the red reflex in non-Caucasian infants is common in primary examinations. Unexplained and persistent lactic acidosis at birth should not be discounted and should be followed up after discharge. Sengers syndrome should be considered as a differential diagnosis in babies who present with congenital cataracts especially if associated with lactic acidosis and later hypertrophic cardiomyopathy.

Keywords: Sengers syndrome; Hypertrophic obstructive cardiomyopathy; Cataract lactic acidosis; *AGK* gene

Abbreviations: HOCM: Hypertrophic Cardiomyopathy; *AGK*: Acylglycerol Kinase; mDNA: Mitochondrial DNA; ED: Emergency Department; FP: Family Physician; CSF: Cerebrospinal Fluid; NIPE: New-born and Infant Physical Examination (NIPE); LV: Left Ventricle; DNA: Deoxyribonucleic Acid; DDS: Depletion Syndrome

Introduction

We report a case of Sengers syndrome with delayed recognition of blunted red eye reflex during two consecutive primary new-born examinations. The Infant Screening Programmer's major aim is to identify and refer all children born with congenital abnormalities of the heart, hips, eyes or testes within 72 hours of birth and further detect those abnormalities that may become detectable by 6-8 weeks of age. Absence of red reflex or blunted red reflex are indication for ophthalmology' referral. In our patient his pale retina was attributed to his darker skin which delayed the diagnosis of Sengers syndrome until he developed severe heart failure.

Sengers syndrome is an autosomal recessive mitochondrial depletion disorder due to loss of function mutation in the *AGK* gene. To our knowledge there are about 40 cases reported to date [1]. The severe form usually presents in the first few weeks of life and is characterized by congenital cataracts, progressive HOCM, skeletal myopathy and lactic acidosis. HOCM is often fatal in first few months of life. Early recognition of this condition can help the survival; hence paediatricians should consider this condition as a differential diagnosis in babies who present with congenital cataracts, particularly if associated with HOCM and lactic acidosis.

Case Presentation

A 4 month old boy was referred to the ED by his GP for few weeks of poor feeding, failure to thrive and a few days of tachypnoea. This was the bronchiolitis season and initial assessment suggested a bronchiolitic illness. However he appeared sweaty, was tachypnoeic at 60 breaths per minute with mild subcostal recession. Auscultation revealed fine crepitation's on both lung bases with grade 2 systolic murmurs. His saturation was 91% in air, had 3 centimeter palpable liver and normal femoral pulses. He also wore aphakic glasses after a recent eye surgery for cataract.

Of note, he is the firstborn of non-consanguineous, healthy parents of Indian origin; there were no abortions, still births or deaths in infancy. A few of the relatives on his paternal side needed cardiac muscle biopsies, but further details in this regard were unavailable. His antenatal scans were unremarkable until 32 weeks following which pregnancy was closely monitored for intrauterine growth retardation. He was born vaginally at term with APGAR scores 6 and 7 at 1 and 5 minutes respectively. He weighed 2.4 Kg, his oxygen saturation remained 88% in air with respiratory rate of 70 per minute in delivery room for which he was subsequently admitted to the neonatal unit for a complete septic screen and intravenous antibiotics. His venous blood lactate and cerebrospinal fluid (CSF) lactate was 13 mmol/L and 8 mmol/L respectively (normal range: 0.5-2.2 mmol/L). Serum ammonia, amino acid and urine organic acid were normal. Chest radiograph, echocardiogram and ultrasound scan of the brain were also unremarkable. His blood and CSF cultures were negative for any bacterial growth. Over the next five days his breathing settled and he established feeding. He was given 5 days course of antibiotics due to initial lactic acidosis. Repeat serum and CSF lactate were 4 and 2 mmol/L respectively; as his metabolic workup was unremarkable he was discharged after a normal newborn examination. His retinal reflex

was slightly prior to this presentation to ED, his health visitor had referred him to GP at 7 weeks of age for reduced feeding and poor weight gain. His parents also had concerns about persistent sweating of head and what they described as "crossed eyes" since birth. There were also concerns about his visual fixation and following. However, his examination was said to be normal and the parents were reassured. 3 weeks later, he re-presented to his GP due to progression of his squint and on this occasion he was found to have absent red eye reflex. An urgent referral to the ophthalmologist was made which confirmed bilateral dense congenital cataracts. He underwent right lensectomy and left anterior viterectomy at 12 weeks of age. He had some improvement in his vision with aphakic glasses postoperatively and no further investigation took place.

The ED blood gas revealed pH 7.32, with a lactic acid of 4.4 mmol/L. Chest radiograph showed massive cardiomegaly (Figure 1). An urgent Echocardiogram was arranged, which demonstrated severe HOCM, with concentric biventricular hypertrophy (Figure 2). Maximal left ventricular (LV) wall thickness was 11 mm with complete mid cavity systolic obliteration and impaired LV relaxation (Figure 3).

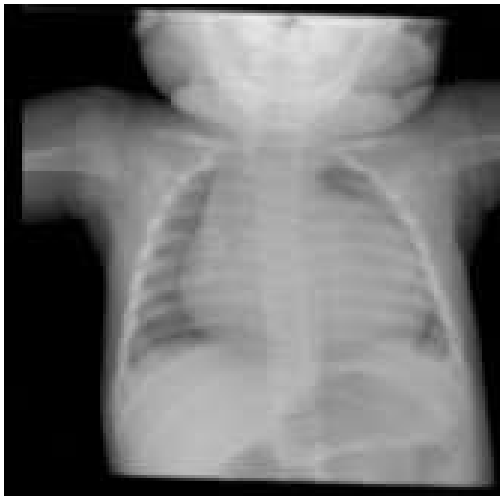

Figure 1: Chest radiograph of the patient showing huge cardiomegaly.

He was transferred to a tertiary cardiac center and was gradually stabilized over next few days by non-invasive ventilatory support, fluid restriction and small doses of propanolol and diuretics. His cardiac output was dependent on a relative tachycardia rather than an increase in his stroke volume due to persisting HOCM. Metabolic screening for cardiomyopathy was performed. Serum levels of Troponin, Creatinine kinase, LDH, Vitamin A, B12, E, Thiamine, Iron, Folate, Acid alpha gluosidase enzyme (for Pompe's diease), Glycosaminoglycans (for mucopolysccharidosis), Biotinidase, Selenium, Zinc, Pyruvate, Ammonia, Free fatty acid, B hydroxybutyrate, Carnitine profile, Amino acid and Urine organic acids were all within normal limits. His thyroid function test, his muscle and skin biopsies showed clear lipid accumulation with no significant change in the cell morphology.

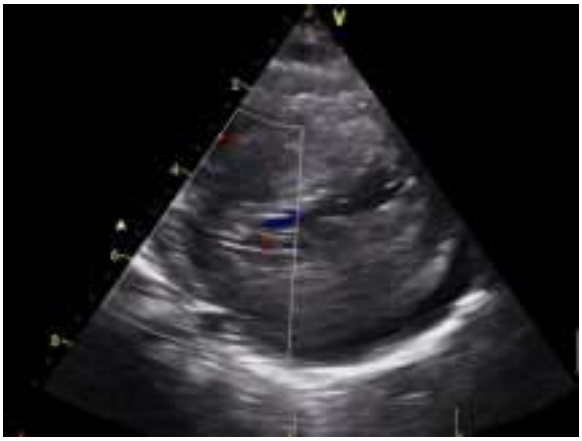

Figure 2: Echocardiogram showing severe HOCM with concentric biventricular hypertrophy with pericardial effusion.

Sequencing of the entire coding region and intron-exon boundaries of the *AGK* gene revealed him to be apparently homozygous for a novel putative splicing mutation, c.1047-2A>G. This substitution has not been previously reported, but is predicted to abolish the consensus acceptor slice site of intron 14 and is therefore highly likely to lead to aberrant splicing of the *AGK* transcript. This result was consistent with a diagnosis of *AGK*-related Sengers syndrome.

Both parents' DNA samples were tested by direct sequencing and both were found heterozygous for novel putative splicing mutation, c. 1047-2A>G in intron 14 of *AGK* gene, confirming the apparent homozygosity in their affected son. Genetic testing has been offered to other relevant family members and prenatal testing will also be available for future pregnancies.

Currently, he is awaiting cardiac transplant. He is followed up by, paediatric cardiologists and a cardiac transplant team. He now remains on finely tuned doses of Frusemide, Spironolactone, Carnitine, Propranolol, Sodium bicarbonate, Iron, Multivitamin supplements, Riboflavin and Co- enzyme Q. He is also on high-energy formula supplemented via a nasogastric tube and is growing above the 50th centile with appropriate neuromotor development at 1 year of age. He can fix and follow with his aphakic glasses.

Discussion

Sengers syndrome, an autosomal recessive disorder, occurs due to a mutation of the *AGK* gene, which is located on the 7th chromosome at 7q34 [1].

Mitochondria are the power houses of the cell. The inner mitochondrial membrane has five respiratory chain enzyme complexes embedded in them, responsible for cellular respiration and ATP production via oxidative phosphorylation. They are genetically controlled by nuclear and mitochondrial genes. *AGK* gene is a nuclear gene which encodes one of the mitochondrial transmembrane enzymes, acylglycerol kinase, that catalyzes the formation of phosphatidic and lysophosphatidic acid which are important phospholipids of mitochondrial membranes [1-3]. Cardiolipin, one of its derivatives is more specific to mitochondrial membrane, has an important role in mitochondrial function and apoptosis [1].

There are nearly 22 nuclear genes responsible for replication and maintenance of mitochondrial DNA (mtDNA). Abnormalities in these can lead to severe reduction in mtDNA content and impaired energy production in affected organs. These are classified as DNA Depletion Syndrome (DDS). Sengers syndrome is a cardiomyopathic type of DDS referred to as type 10 [4].

Sengers syndrome was first described by Sengers et al. in 1975 where he reported 7 children with congenital cataract and mitochondrial myopathy of skeletal and heart muscle with lactic acidosis [5]. There are a few reports of nervous system involvement with delayed motor development, cerebellar hypoplasia, basal ganglia calcification and cerebral infarction [6].

There are two forms of Sengers Syndrome reported. The severe form due to homozygous *AGK* nonsense mutation is characterized by early onset cataract, lactic acidosis and HOCM that results in death in infancy. Nearly half of the reported cases have died in the first 3-4 months of life [3]. The milder form has at least one *AGK* splice site variant, has a better prognosis and develops cardiomyopathy at later stages, with survival into their fourth decade. The mildest form reported had only cataracts [3].

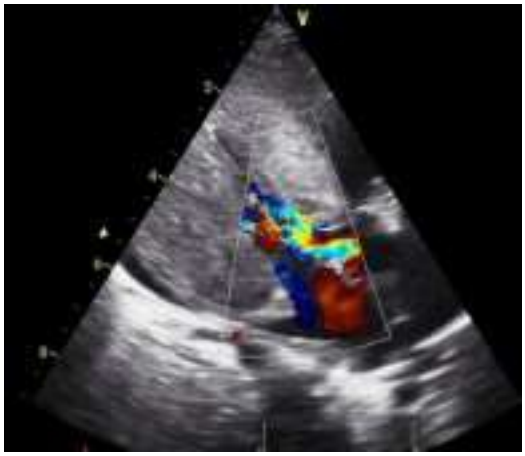

Figure 3: Doppler Echocardiogram showing maximal left ventricular (LV) wall thickness of 11 mm with complete mid cavity systolic obliteration and impaired LV relaxation.

Congenital cataracts are one of the hallmarks of this condition. The bilateral lens opacification may manifest as leucocoria at birth or in first few weeks. Treatment is in the form of lens extraction. Vision is generally compromised postoperatively by nystagmus and strabismus. Axial myopia is common and they may develop myopic fundal changes requiring less than +10 diopters of aphakic correction. Other changes like pale optic disks, pigmentary retinopathy and mild dyschromatopsia have also been noted. The electroretinography may show diminished rod and cone functions [7]. Disturbed membrane-lipid composition due to *AGK* deficiency has been attributed for the cataract. The cellular architecture and arrangement are critical for light transmission and lens transparency [1,3]. Energy depletion and resulting sarcomeric dysfunction in cardiac muscle leads to (possibly compensatory) hypertrophic cardiomyopathy with abnormalities of mitochondria and storage of lipid and glycogen [3]. Defective *AGK* leads to anaerobic respiration and lactic acidosis with minimal muscular exertion [3].

Conclusion

Although Sengers syndrome is a rare disorder, we suggest that it should be considered in the differential diagnosis in patients who present with congenital cataracts in presence of hypertrophic cardiomyopathy, with or without lactic acidosis.

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