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Russell silver syndrome with alkaptonuria in a child - A case report

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Abstract

Russell–Silver syndrome is a clinically and genetically heterogeneous disorder mainly characterized by severe intrauterine and postnatal growth retardation and relative macrocephaly, a typical triangular face, asymmetry, feeding difficulties. About 55% of RSS patients present a loss-of-methylation of the paternal ICR1 domain on chromosome 11p15. (1). Maternal uniparental disomy for chromosome 7 (mUPD7) is found in 5–10% of cases. In 1–2% of RSS patients, (sub)microscopic chromosomal aberrations can be observed. The diagnostic workup should therefore include methylation/genomic testing for chromosome 11p15, UPD (7) mat analysis and molecular karyotyping. Alkaptonuria (AKU) is a rare disorder of autosomal recessive inheritance. It is caused by a mutation in a gene that results in the accumulation of homogentisic acid (HGA). Characteristically, the excess HGA means sufferers pass dark urine, which upon standing turns black, diagnosed by liquid chromatography tandem mass spectrometry.

Keywords: SRS, dark urine, IUGR, alkaptonuria, ochronosis

Introduction

Russell-Silver syndrome (RSS) is characterised by intrauterine and postnatal growth retardation, asymmetry of the limbs, clinodactyly, and various facial dysmorphic features, such as a triangular face with a small lower jaw, low-set ears and frontal bossing. The growth failure in RSS is frequently associated with failure to thrive and very low body mass index. Many RSS children have

significant feeding difficulties. Craniofacial symptoms include a characteristic small, triangular face with a prominent forehead and micrognathia, downturned corners of the mouth and ear anomalies. In more than 50% of patients, limb and body asymmetry is present. A growing number of chromosomal aberrations have been associated with RSS but only chromosomes 7, 11, 15, and 17 have been consistently involved in individuals fulfilling strict diagnostic criteria of RSS. Alkaptonuria (AKU) is a rare disorder of autosomal recessive inheritance. It is caused by a mutation in a gene that results in the accumulation of homogentisic acid (HGA). Characteristically, the excess HGA means sufferers pass dark urine, which upon standing turns black. This is a feature present from birth. Over time patients develop other manifestations of AKU, due to deposition of HGA in collagenous tissues, namely ochronosis and ochronotic osteoarthropathy. Although this condition does not reduce life expectancy, it significantly affects quality of life.

Case report

A case of 22 months old male child was admitted in the Paediatrics department with chief complaint of vomiting since 1 week with fever and passing loose stool since last 2-3 days. There was 3-4 episodes of vomiting per day which was non-bilious and non-projectile associated with fever which was low grade, undocumented, intermittent, no diurnal variation. The child was active in intrafebrile period. There was 3-4 episodes of passing loose stools per day, semisolid consistency, foul smelling, mucus present. The child was 2nd order born to non-consanguineous marriage Hindu chindaliya residing at Nerul hailing from Noida with significant birth history of full term IUGR delivery via spontaneous vaginal delivery in hospital, baby cried immediately after birth with birth weight of 2050g admitted in NICU in view of respiratory distress and one episode of hypoglycemia. He was kept on oxygen by hood and gradually off oxygen was done after 5 days and discharged on 7th day of life. At 3-4 months of age, the mother noticed reddish coloured urine which leaves dark stain on clothes after some time which didn't go away after washing. At 7-8 months of age, mother noticed there was inadequate weight and height gain and he was not attaining milestones according to the age. There was no history of altered sensorium, convulsion, feeding difficulty, lethargy. There was no significant family history. At one year of age, he was worked up at bai jerbai Wadia hospital, Mumbai, Complete blood count , random blood glucose, serum calcium, electrolytes, thyroid function test , liver function test, lipid profile were done in which haemoglobin was 10.4g/dl (microcytic hypochromic anaemia with anis poikilocytosis) , CPK level of 242 U/L, triglyceride level were raised 219mg/dl, G6pd level checked which was normal Then IEM work up – urine gas chromatography mass spectrometry screening report and tandem mass spectrometry screening report raised homogentisic acid suggestive of alkaptonuria. Parents were counselled about the disorder and dietary advise given. MRI brain suggested of hypoxic ischemic injury with periventricular white area hyper density. Parents noticed that he looks different from the elder sibling and other family members.

He was immunized till 9 months of age according to NIS, no additional vaccination taken. He was non-vegetarian with deficit of almost 600 kcal and 4g protein. Developmentally, he cruises through furniture which is gross development quotient of 45%, imitates scribbling which is finer motor DQ of 68%, socially achieved 100% as he handles spoon well and engage in parallel play and

he babbles which is 13.6%, so he only preserved social milestone. His overall DQ was 56.6% which refers to global developmental delay.

On general physical examination, he was conscious, poorly built and nourished with dysmorphic features. He was vitally stable with mild pallor. Anthropometrically he was PEM grade III with microcephaly, upper segment to lower segment – 0.86 which was low according to age.

In head to toe examination , frontal prominence with sparse hair and small triangular facies, left low set ear , depressed nasal bridge, absent philtrum, downturned corners of mouth , absent nasolabial fold, open mouth ,high arch palate, low posterior hair line , pectus excavatum, Mongolian spot , hyperpigmented patches covering whole back, clinodactyly of 5th finger of both hand, left talipes varus present which fulfil clinical criteria of Russell silver syndrome .There was no other significant finding present in the systemic examination.

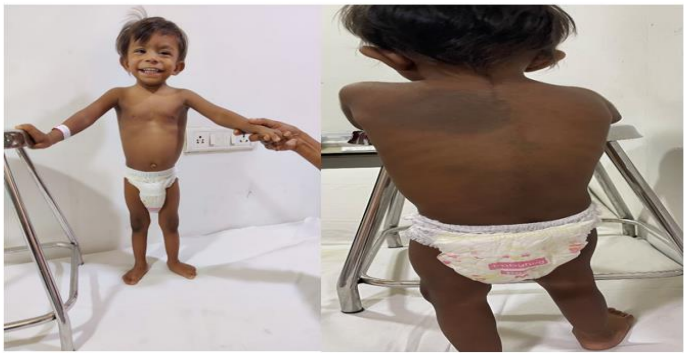

Figure 1

Symptomatic treatment was given. Ophthalmology reference was given which showed he had left iris coloboma and bilaterally minimal tortuous retinal vessels for which no management to be done. BERA was done which was within normal limit, 2D ECHO suggestive of minimal pericardial effusion for which no active intervention needed. Occupational therapy started in which they advised them to get AFO braces shoes and walking reps were started. He was asked to have low protein(tyrosine) and high carbohydrate diet. Genetic counselling was done. It is diagnosed Clinically but for confirmation molecular testing and DNA methylation analysis are done but false negative result doesn't exclude the diagnosis.

Figure 2

Discussion

Russell–Silver syndrome/Silver–Russell syndrome is a clinically and genetically heterogeneous disorder mainly characterized by severe intrauterine and postnatal growth retardation. The growth failure in RSS is frequently associated with failure to thrive and very low body mass index. Many RSS children have significant feeding difficulties. Craniofacial symptoms include a characteristic small, triangular face with a prominent forehead and micrognathia, downturned corners of the mouth and ear anomalies. (2) In more than 50% of patients, limb and body asymmetry is present. only moderate but significant impairments in cognitive outcome in comparison with their siblings. Genetic and epigenetic disturbances can meanwhile be detected in approximately 50% of patients with typical RSS features. Up to 5% of patients carry a maternal uniparental disomy of chromosome 7 (UPD (7) mat), at least 44% show hypomethylation in the chromosome 11p15 imprinting center 1 (IC). In 1–2% of RSS patients, (sub)microscopic chromosomal aberrations can be observed. The diagnostic workup should therefore include methylation /

genomic testing for chromosome 11p15, UPD (7) mat analysis and molecular karyotyping. The recurrence risk is generally low in RSS but it can be strongly increased in cases of familial epimutations or a chromosomal rearrangement. Interestingly, in 7% of cases with chromosome 11p15 hypo methylation, hypomethylation of additional imprinted loci can be detected. Clinically, patients with hypomethylation at multiple loci do not differ from those with isolated 11p15 hypomethylation whereas the UPD (7) mat patients generally show a milder phenotype. (3)

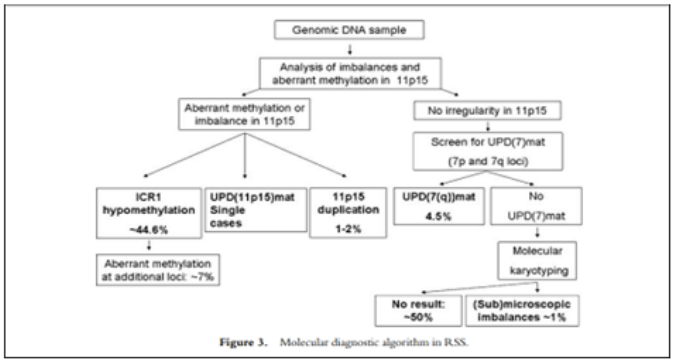

Figure 3. Molecular diagnostic algorithm in RSS.

Clinical features of Russell silver syndrome

- Growth retardation (intrauterine and postnatal)
- Triangular facies
- Excessive early childhood sweating
- Late closure of anterior fontanel
- Limb asymmetry
- Cafe´ au lait spots
- Achromia
- Down-curving corners of mouth
- Fifth-finger clinodactyly
- Blue sclera
- Fasting hypoglycemia
- Genital dysmorphia

It is diagnosed clinically but for confirmation molecular testing and DNA methylation analysis is done but false negative result doesn't exclude the diagnosis.

Net chine-Harbison Clinical Scoring System (NH-CSS) is used. If 4 out 6 criteria present then it is diagnosed clinically.

Clinical criteria	Definition
SGA (birth weight and/or birth length)	≤−2 SDS for gestational age
Postnatal growth failure	Height at 24 ± 1 months ≤−2 SDS or height ≤−2 SDS below mid-parental target height
Relative macrocephaly at birth	Head circumference at birth ≥1.5 SDS above birth weight and/or length SDS
Protruding forehead*	Forehead projecting beyond the facial plane on a side view as a toddler (1–3 years)
Body asymmetry	LLD of ≥0.5 cm or arm asymmetry or LLD <0.5 cm with at least two other asymmetrical body parts (one non-face)
Feeding difficulties and/or low BMI	BMI ≤−2 SDS at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation

Growth hormone (GH) has been proven to have a beneficial effect on the growth of children born with IUGR and consequently in children with RSS. GH treatment may cause an increase in the growth spurt amplitude of patients if it is started prior to puberty. (3,4)

Alkaptonuria is a hereditary disorder and results from absence of homogentisate 1,2 dioxygenase (HGD), the enzyme, predominantly produced by hepatocytes in the liver and within the kidney, is responsible for the breakdown of HGA; an intermediate in the tyrosine degradation pathway. Characteristic early clinical presentation is the observation that urine darkens on standing. This is because the HGA polymerizes but can also be observed upon the addition of alkali substances. (5). AKU has three distinct clinical features; homogentisic aciduria, ochronosis, and ochronotic osteoarthropathy (6-9) Each feature presents at various stages in life, the earliest being detection of HGA in urine. (10). Many therapies have been tried. However, currently as there is no effective therapy, the

management of AKU remains palliative and involves physiotherapy, joint replacement surgery, and pain control. Ascorbic acid (ASC), more commonly known as vitamin C, is an antioxidant believed to reduce the conversion of HGA to BQA via oxidation. However, investigation revealed that although ASC reduced the HGA to BQA conversion, it did not affect HGA urinary excretion. (11). Low protein diet is generally helpful.

Conclusion

SRS is a skeletal and growth condition that is highly morbid. To prevent joint abnormalities, early diagnosis and therapy are crucial. The treatment for particular risk factors can be guided by the identification of the underlying molecular subtype. A multidisciplinary approach to management should be used, as should strict parental supervision. To lengthen limbs, growth hormone, and in more serious situations, surgery, are required. Additionally recommended in SRS are nutritional support and physical therapy. Meticulous history and examination and radiological investigation can confirm the diagnosis.

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