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Case Report

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FINCA syndrome

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ABSTRACT

FINCA (fibrosis, neuro-degeneration, cerebral angiomatosis) syndrome is a rare autosomal recessive early onset fatal disorder characterised by progressive cerebropulmonary symptoms, malabsorption, progressive growth failure, recurrent infection, chronic haemolytic anaemia and transient liver dysfunction. A 5 year old female baby born as a preterm 33 weeks (2nd twin of dichorionic diamniotic twin) to nonconsanguineous parents via intra-cytoplasmic sperm injection and surrogacy, delivered by emergency caesarean section (indication- pre-eclampsia in mother) with a birth weight of 1.8 kg. She had a stormy neonatal period and had anaemia requiring blood transfusion. Developmental delay was noted from early infancy which was not responding to developmental therapy, along with recurrent episodes of aspiration pneumonia. Her twin on the other hand had normal mile stones without any remarkable medical history. Examination and evaluation revealed features of chronic hemolysis. In view of constellation of developmental delay, recurrent infection, chronic hemolytic anaemia and cerebral atrophy beyond documented perinatal issues and dysmorphism, clinical exome sequencing was done which revealed missense variation in exon of NHLRC2 gene on chromosome 10 suggestive of FINCA syndrome. This case emphasized the need of genetic testing to resolve uncertainty in etiology and accurate prognostication.

Keywords: Cerebropulmonary syndrome, NHLRC2, Developmental delay

INTRODUCTION

FINCA (fibrosis, neurodegeneration, cerebral angiomatosis) syndrome, first reported in 2018, is a progressive brain-lung disease (OMIM 618278) caused by a variation in the NHLRC2 gene.[1] FINCA syndrome is inherited in an autosomal recessive manner. What starts with neurological symptoms manifesting initially, is followed by involvement of multiple organs as the disease progresses, such as severe tissue fibrosis, neurodegeneration and cerebral haemangioma.[2] Common manifestations comprise of pulmonary fibrosis with episodes of respiratory distress, developmental delay, muscular hypotonia, dystonia, seizures and brain atrophy. Progression of disease results in early demise.[1]

The exact function of NHLRC2 cytosolic protein and how its dysfunction might result in this specific multi-organ failure is currently unknown[3]. Its expression is in multiple tissue. Respiratory disorder often follows progressive worsening and aggravations by infectious and at times non-infectious causes.[4]

All children reported with this syndrome had neurologic abnormalities such as global developmental delay, axial hypotonia and dystonia.[4] Magnetic resonance imaging identified global cerebral atrophy and aberrant angiomatosis as an inconsistent finding.[5] Most children reported gastrointestinal problems identified by episodic diarrhoea, often chronic and associated failure to thrive.[5] Several other organs were affected, including the liver.

CASE REPORT

Clinical description

5 year old female baby born as a preterm 33 weeks (2nd twin of DCDA twin) to non-consanguinous parents via intracytoplasmic sperm injection and surrogacy by emergency LSCS (indication- pre-ecclampsia in mother) with a birthweight of 1.8 kg. Baby had a stormy neonatal period-sepsis, NEC, feed intolerance, PDA, Neonatal hyperbilirubinemia, anemia requiring blood transfusion and NICU stay for 14 days. She also exhibited developmental delay from the age of 1 month, starting with truncal hypotonia in combination with peripheral hypertonia and hyperreflexia in the lower limbs not improving with developmental therapies, and recurrent episodes of aspiration pneumonia. She developed first episode of seizure (generalised tonic type), when she was 2 1/2 months old. Over the next 18-20 months, she had increased frequency of seizures for which antiseizure medications were given. By the age of three years her pulmonary situation stabilized. Brain MRI revealed diffuse cerebral atrophy, no abnormal elevations or altered ratios on MR Spectroscopy. EEG done was grossly abnormal with right sided predominance and burst suppression pattern suggestive of modified hypsarrythmia. At the age of 5, infections became less frequent (1-2 times a year). Focal and generalized seizures were controlled with antiseizure medications (levetiracetam, valproate). There is no evidence of malabsorption, hepatic and cardiovascular involvement at present. In view of constellation of features like hemolytic anemia and cerebral atrophy beyond documented perinatal issues and dysmorphism, clinical exome sequencing revealed missense variation in exon of NHLRC2 gene on chromosome 10.

Management and outcome

Her initial investigations revealed hemoglobin- 11.2 g/dl, packed cell volume- 32%, MCV-90.9 fl, mean corpuscular hemoglobin- 33 pg, mean corpuscular hemoglobin concentration-36.3 g/dl, red cell distribution width- 23.1 fl, reticulocyte count- 0.8%. Total bilirubin- 3.0 mg/dl, direct bilirubin- 0.37 mg/dl, aspartate transaminase/alanine transaminase- 43/37 U/l, ALP- 221 U/l, sodium- 139 meq/l, potassium- 4.3 meq/l. Coombs test done was negative.

Metabolic screening was negative. G6PD level was normal. Peripheral blood smear showed -moderate to marked anisopoikilocytosis with features of mild hemolytic process. The child was given supportive treatment, antiseizure medications, occupational therapy and physiotherapy. The parents were counselled regarding genetic inheritance of the disease.

Table 1: Clinical exome sequencing report.

Gene (transcript)#	Loc-ation	Variant	Zygosity	Disease (OMIM)	Inherita-nce	Classification
NHLRC2(+) (ENST00000369301.3)	Exon 3	c.601del (p.Arg201GlyfsTer11)	Hetero-zygous	Fibrosis, neuro-degeneration, and cerebral angiomatosis (FINCA) syndrome	Auto-somal recessive	Pathogenic
		c.442G>T (p.Asp148Tyr)				Likely Pathogenic

#- Likely compound heterozygous variants causative of the reported phenotype were identified.

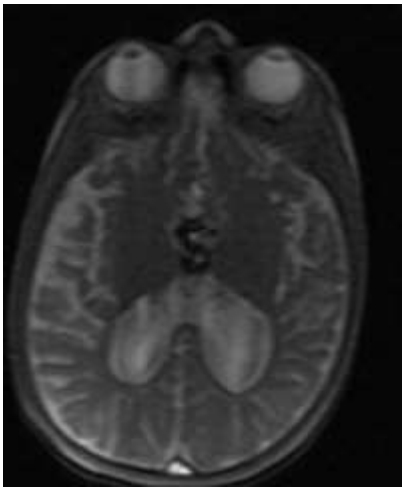

Figure 1: Radiological evaluation- diffuse cerebral atrophy.

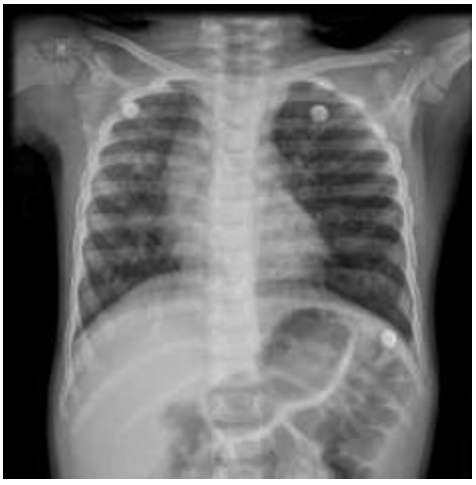

Figure 2: Radiological evaluation- bilateral pulmonary infiltrates.

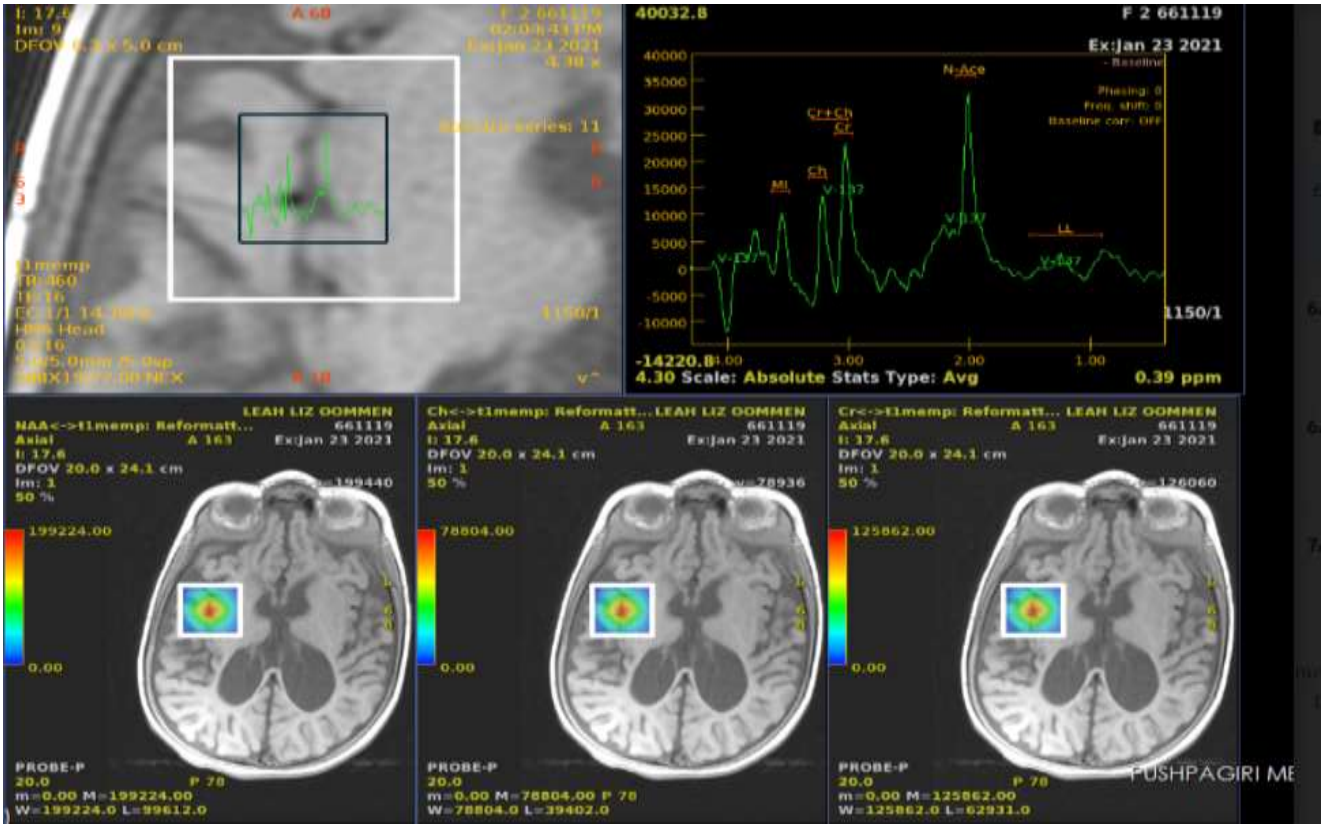

Figure 3: Radiological evaluation- no abnormal elevation or altered ratios.

DISCUSSION

FINCA is a rare early onset fatal disorder with Autosomal recessive inheritance characterized by progressive cerebropulmonary symptoms, malabsorption, progressive growth failure, recurrent infections, chronic hemolytic anemia and transient liver dysfunction secondary to variations in the NHLRC2 gene.[1] The gene is located on chromosome 10 (Chr 10q25.3) consisting of 11 exons and 10 introns.[6] NHLRC2 protein is present is in several cell types and regions of the human brain and participates in the cellular organization and is responsible for regulating the cytoskeleton and vesicular transport.[7] NHLRC2 has been indicated to have function in mediating fibroblast differentiation, regulating generation of reactive oxygen species, cellular apoptosis, and T-cell lymphocyte homeostasis.[5] Thus, pathology in the NHLRC2 gene could cause uninhibited tissue fibrosis and, therefore, can induce differentiation of fibroblasts to myofibroblasts.[8]

The relation between FINCA syndrome and calvarial red bone marrow hyperplasia, is unclear. This phenomenon is known to appear in response to red blood cell disorders, iron deficiency anemia, or hemolytic disorders.[7]

The neuropathological findings of the patients include brain atrophy, vacuolar neurodegenerative diseases, loss of myelin with glioma, cerebral hemangioma, and neuronal loss in the anterior horn of the spinal cord.[6]

At present, there are very few cases worldwide on FINCA syndrome (around 15 as of 2023), and the reported cases were diagnosed when patients developed relevant symptoms after 2 months of age, and there is no relevant report on the early manifestations of FINCA syndrome that may occur in the neonatal period. Patients with FINCA have multi-organ symptoms, which can be manifested along with feeding problems, growth failure, chronic diarrhoea, malabsorption, recurrent bronchopulmonary infections, seizures, and lung fibrosis, leading to progressive respiratory failure. Patients described by the Finnish and Ukrainian group, and two patients described by Rapp et al died before reaching the age of 3.[1,5,9] The respiratory disorder in all patients was progressive or exacerbated during infections. The remaining four patients of Rapp et al survived into late childhood.[5] The oldest patient described so far in literature is 14 years old.[5]

CONCLUSION

This case emphasizes the need of genetic testing to resolve uncertainty regarding underlying etiology and accurate prognostication. Our findings contribute to the phenotypic expansion of FINCA syndrome. We suggest that FINCA syndrome should be considered in individuals of all age groups who present with primary neurodevelopmental delay and a history of child that improved over time.

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