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CASE REPORT

A Rare Genetic Cause of Pediatric Interstitial Lung Disease and immunodeficiency: Identifying FINCA Syndrome

Abdelbari M^a, Bouguila J^a, Tej A^a, Jaballah N^a, Soyah N^a,
 Tilouche S^b, Kebaili R^a, Boughammoura L^a

^a Pediatric ward, Farhat Hached university hospital, Tunisia

^b Pediatric resuscitation ward, Farhat Hached university hospital, Tunisia

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 immunodeficiency, genetic,
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Abstract

Background: Fibrosis, Neurodegeneration, and Cerebral Angiomatosis (FINCA) syndrome is a recently described multisystem disorder primarily affecting infants, often with poor respiratory prognosis. It is caused by mutations in the *NHLRC2* gene. While clinical presentation typically includes progressive cerebro-pulmonary symptoms, growth failure, and malabsorption, there is significant phenotypic variability among the few cases reported worldwide. Interstitial lung disease (ILD) and immune dysfunction are increasingly recognized as critical, yet under-reported, manifestations of this syndrome.

Case Presentation: We report a novel case of FINCA syndrome in an 18-month-old boy of north african descent, presenting with a new pathogenic variant. The patient experienced recurrent episodes of acute respiratory distress, exacerbated by uncoordinated swallowing (aspiration) and pulmonary superinfections. Over time, progressive dystonia and neurological decline became prominent, with neuroimaging revealing cortical and subcortical atrophy. Notably, the clinical course was marked by recurrent infections, including two occurrences of fungal skin abscesses, providing strong evidence of the immunodeficiency associated with certain *NHLRC2* variants.

Conclusion: This report contributes to the clinical and genetic expansion of FINCA syndrome by identifying a novel variant and emphasizing its role as a rare etiology of both pediatric interstitial lung disease and primary immunodeficiency. Our findings underscore the importance of multisystemic screening in children presenting with concomitant neurological and respiratory decline.

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* Auteur correspondant : Abdelbari Marwa

Adresse e-mail : marwa.abdelbari1@gmail.com / marwa.abdelbari@FAMSO.u-sousse.tn

Introduction

Rare diseases are characterized by significant genetic and clinical polymorphism. Fibrosis, neurodegeneration, and cerebral angiomas (FINCA) syndrome was first described in patients presenting with severe respiratory distress syndrome associated with poor clinical outcomes. Most affected individuals exhibit a multisystemic involvement, predominantly characterized by a progressive interstitial lung disease that is frequently exacerbated by recurrent infections [1–3]. Interstitial lung disease and increased susceptibility to infections have been identified as the primary causes of mortality before the age of three years. To date, novel variants continue to be reported, suggesting that clinical phenotypes vary according to specific genetic mutations [4].

Observation

We report the case of an 18-month-old boy admitted to the pediatric ward for dyspnea. He was born to consanguineous parents. The family history revealed that a sister had died at two years of age from acute respiratory distress syndrome (ARDS) secondary to the H1N1 virus. The patient remained asymptomatic until the age of 15 months, when he began experiencing recurrent episodes of acute dyspnea. Physical examination revealed weight stagnation coinciding with respiratory symptoms, with no dysmorphic features. The child was polypneic, though pulmonary auscultation was unremarkable. He frequently required high-flow nasal cannula (HFNC) oxygen therapy.

His respiratory status markedly deteriorated on three occasions, leading to a diagnosis of severe pediatric acute respiratory distress syndrome (PARDS). Each episode was consistently preceded by uncoordinated swallowing, raising suspicion of a tracheoesophageal fistula. However, this was ruled out by a normal upper gastrointestinal (GI) series and rigid bronchoscopy. Transthoracic echocardiography was normal. Chest computed tomography (CT) demonstrated diffuse, bilateral ground-glass opacities without parenchymal consolidation, associated with subpleural reticulations in the right lower lobe (Figure 1).

Laboratory investigations showed mild anemia (Hb: 8.9 g/dL, MCV: 75 fL, MCH: 25 pg) with slight regeneration, and normal white blood cell and platelet counts. The direct antiglobulin test was negative, and lactate dehydrogenase (LDH) was mildly elevated (400 UI/L). Microbiological cultures obtained during mechanical ventilation were negative for specific pathogens. Weaning from ventilation was achieved after an average intubation period of seven days. Radiological

findings during exacerbations were consistent with bronchoalveolar superinfections, which responded well to broad-spectrum antibiotics. Additionally, the patient twice developed a lower limb skin abscess; microbiological analysis confirmed a fungal etiology (*Candida albicans*). Furthermore, the patient exhibited a marked susceptibility to nosocomial infections, predominantly involving the respiratory tract, which further reinforced the suspicion of an underlying primary immunodeficiency. Despite this clinical presentation, immunological investigations—including quantitative immunoglobulin assays and cellular immunity studies (T and B cell subsets)—yielded normal results. This discrepancy between clinical susceptibility and normal routine immune screening guided the diagnostic focus toward more complex genetic syndromes.

A sweat test showed normal chloride levels (15 mmol/L). A neuromuscular disorder was suspected due to recurrent aspiration episodes and muscle wasting; over time, peripheral hypertonia was noted. Electromyography (EMG) was unremarkable, but brain and spinal cord magnetic resonance imaging (MRI) revealed unexpected subcortical parenchymal atrophy without focal lesions. Whole exome sequencing (WES) identified a homozygous variant in the *NHLRC2* gene: c.1507G>T (p.Asp503Tyr), classified as a Class 3 variant of uncertain significance (VUS).

Discussion

The vast majority of interstitial lung diseases (ILD) remain classified as idiopathic. In 1979, an initial cohort study of 100 pediatric lung biopsies identified non-specific or idiopathic fibrosis as the most prevalent histological finding. Other described lesions included pulmonary hemosiderosis, lipoidosis, and alveolar microlithiasis, alongside specific inflammatory etiologies such as tuberculosis, syphilis, or foreign body aspiration (5).

In 2008, a landmark European Respiratory Society (ERS) publication refined the classification of childhood ILD (chILD), distinguishing between disorders prevalent in infancy and those more common in older children. This framework highlighted critical diagnoses to be excluded during infancy, notably neuroendocrine cell hyperplasia of infancy (NEHI), genetic defects in surfactant metabolism, and disorders of lung growth and development (5). Furthermore, familial idiopathic forms are not uncommon, with a reported prevalence ranging from 1.3 to 5.9 per million (6).

Clinical presentation of chILD typically includes tachypnea, hypoxemia, chest wall retractions, crackles, and failure to thrive (7). However, these manifestations lack specificity, particularly during the first two years of life, where they may overlap with more common conditions such as airway malacia or pathological gastroesophageal reflux (8).

Among these rare entities, FINCA syndrome is an exceedingly rare condition, with only a few dozen cases documented in the literature. It is caused by mutations in the *NHLRC2* (NHL repeat-containing protein 2) gene. First described in 2018 in three Finnish children who died before the age of two, this syndrome marked the first instance where *NHLRC2* mutations were linked to human disease. The original Finnish cohort carried the heterozygous variant p.Asp148Tyr (9).

In 2020, Brodsky et al. described a novel compound heterozygous variant in a patient presenting with clinical features broadly consistent with previously reported FINCA cases. However, a comparative analysis with the original Finnish cohort revealed distinct chronological differences: the Finnish patients exhibited an earlier onset of progressive respiratory disease, characterized by the premature development of bilateral ground-glass opacities and interstitial infiltration (3). This novel compound heterozygous variant aligns more closely with our current case, as initial respiratory symptoms emerged at 15 months, and the sibling's death occurred at age two, precipitated by H1N1 viral pneumonitis. Subsequent studies have significantly expanded the phenotypic spectrum of FINCA syndrome, demonstrating considerable variability in clinical severity, particularly regarding the extent of respiratory lesions and the prevalence of recurrent infections as indicators of underlying immunodeficiency (10).

Recent genetic data from 2021 have further corroborated this phenotypic heterogeneity, mapping specific clinical presentations to various *NHLRC2* variants. While neurological findings, including global neurodevelopmental delay, axial hypotonia, and dystonia, remained near-universal (2), failure to thrive and immune system dysfunction were reported less frequently. Notably, our patient presented with a clinical history marked by recurrent infections; the occurrence of a fungal skin abscess was particularly suggestive of impaired immune surveillance.

To date, 28 cases of FINCA syndrome have been documented in the literature. In 2023, Uusimaa's team expanded this series by reporting four additional patients who shared the hallmark

clinical features of the syndrome. Among them, one patient was homozygous for the pathogenic variant c.442G > T, while the others were compound heterozygous for this variant and two alternative pathogenic *NHLRC2* mutations. Clinical outcomes varied significantly: two cases were fatal, whereas respiratory function stabilized in the remaining patients (11). Genetic analyses identify p.(Asp148Tyr) as the most frequent variant (12). Henrike et al. suggested that the combination of the recurrent p.(Asp148Tyr) missense variant with a truncating variant is strongly associated with severe pulmonary involvement. In contrast, individuals homozygous for this variant typically did not exhibit respiratory symptoms and generally presented with a more attenuated clinical phenotype (12).

Conclusion

In conclusion, this case contributes to the ongoing expansion of the known phenotypic spectrum of FINCA syndrome and underscores its significance as a critical, albeit rare, etiology of pediatric interstitial lung disease and immunodeficiency. Our findings highlight the necessity of maintaining a high index of suspicion when encountering the triad of progressive respiratory distress, recurrent aspiration episodes (false paths), and clinical markers of immunodeficiency. By integrating these multisystemic manifestations into the diagnostic workup, clinicians may achieve earlier identification of *NHLRC2*-related disorders. Ultimately, further research into the molecular mechanisms of this syndrome remains essential to better understand its clinical variability and to refine management strategies for affected children.

Declarations:

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images

Availability of data and materials: All data generated or analysed during this study are included in this published article

Competing interests: No conflict of interest

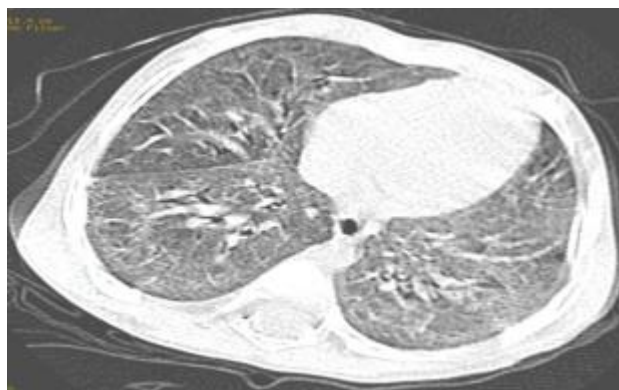


Figure 1: Axial chest CT scan showing bilateral interstitial opacities and parenchymal abnormalities.

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