Journal of Radiology Medicine in

Case Report

Doi: 10.51271/JRM-0030

The many radiologic faces of filamin A mutation in 2-year-old girl: a case report

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Received: 27.03.2025 ◆ **Accepted**: 15.04.2025 ◆ **Published**: 26.04.2025

Cite this article: Özkale Yavuz Ö, Şen Akova B. The many radiologic faces of filamin A mutation in 2-year-old girl: a case report. *J Radiol Med.* 2025;2(2):39-42.

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ABSTRACT

In this article, we present the case of a 2-year-old girl with filamin A (FLN-A) mutation who exhibited thrombocytopenia, corpus callosum hypoplasia with periventricular nodular heterotopia (PNH), bicuspid aortic valve, mild pulmonary hypertension, bilateral lung hyperinflation, and gastroesophageal reflux. FLN-A is an actin-binding protein, expressed throughout the body that has several functions in cell signaling and preservation of cell shape and migration. Mutation in the FLNA gene is associated with a diverse array of disorders, including neuronal migration abnormality, and anomalies of connective and vascular tissue. Abnormal FLNA interactions can affect pulmonary viscoelastic properties, disrupt alveolar formation and growth, and cause alveolar growth abnormalities, leading to alveolar simplification, emphysematous changes, and pulmonary arteriopathy. In addition, defects in cell migration during embryonic development is also another mechanism of the development of congenital cortical malformations and lung abnormalities. The patient was presented with vomiting, desaturation during feeding, a need for supplemental oxygen, and cyanosis. Computed tomography imaging revealed the presence of lung disease with lung hyperinflation, and pulmonary hypertension. Additionally, cerebral PNH and corpus callosum hypoplasia, and gastroesophageal reflux were also identified by different imaging modalities. This case highlights the significance of various imaging findings in facilitating the early diagnosis of FLNA mutations and underscores the necessity of genetic testing. It also enhances our understanding of the wide spectrum of conditions associated with this mutation.

Keywords: Filamin A mutation, heterotopia, lung disease, children

INTRODUCTION

Filamins are one of the critical actin-binding cytoskeletal proteins that contribute significantly to the formation and maintenance of cellular architecture and morphology. They play essential roles in processes such as cell signaling and transcription, and their expression is observed across various tissues in the body.[1,2] Notably, mutations in filamin A (FLN-A) can lead to a range of developmental malformations affecting multiple organ systems in children. These mutations are particularly associated with defects in neuronal migration, vascular function, and the integrity of connective tissues.[3]

Macrothrombocytopenia frequently presents alongside the FLN-A mutation, which leads to the early release of fragile and immature platelets with a shortened lifespan.[4] Mutations in the FLN-A gene lead to myxomatous mitral valve disease, non-syndromic mitral valve dystrophy, familial Ebstein's anomaly, and prolapsed atrioventricular valves.[5,6] Pulmonary manifestations consist of a wide range of pulmonary disorders that occur during early childhood and include neonatal respiratory failure, severe bronchopulmonary dysplasia, congenital emphysema, atelectasis, interstitial lung disease, recurrent respiratory infections, and pulmonary hypertension.[6-8] Reduced intestinal motility, and congenital idiopathic intestinal pseudo-obstruction often with microcolon are the gastroenterological findings that are frequently described.[9] Periventricular nodular heterotopia (PNH) at the lateral ventricular rim, large cisterna magna, and hypoplasia of the cerebellum and corpus callosum are strongly associated with FLN-A mutations.[10,11]

In the pediatric literature, a significant proportion of studies have focused on clinical perspectives concerning specific systems, including neurological, respiratory, cardiovascular, and musculoskeletal systems.[1,2,5-13] There are also articles that exclusively evaluate adult populations.[5,14,15] To our knowledge, FLN-A mutation-associated multisystem involvement has not been reported radiologically before.

CASE

A 2-year-old girl was admitted to the emergency department due to vomiting and acute respiratory distress. Upon evaluation, she exhibited peroral cyanosis, and desaturation while feeding and heart murmur. The baby (third child of consanguineous parents) was born via cesarean section at 37 weeks of gestation, with a birth weight of 2140 grams. The two years of her life was unremarkable. The family had no history of genetic or metabolic diseases or congenital disorders. On admission, the physical examination confirmed signs of respiratory distress, peroral cyanosis, a heart murmur, poor weight gain, and joint laxity. Laboratory investigations revealed thrombocytopenia (124 x10^3/ml) and coagulopathy. An echocardiogram showed the presence of a bicuspid aortic valve, patent ductus arteriosus, and mild pulmonary hypertension, with a mean pulmonary arterial (PA) pressure of 20 mmHg, which is near the threshold for pulmonary hypertension. The child's condition deteriorated with worsening respiratory distress; the child was unable to maintain saturation even with oxygen support. An AP chest radiograph showed nonspecific bilateral fibroatelectatic areas. A chest computed tomography (CT) scan revealed hyperinflation of the anterior segments of both lungs, along with subsegmental atelectasis and pleuroparenchymal fibrotic changes (**Figure 1**) in the posterior segments. Indeed, the ratio of the main pulmonary artery (pulmonary trunk) to the ascending aorta was recorded at 1.3 (**Figure 1**), surpassing the critical threshold of 1.09, which correlated with elevated PA pressure. After stabilizing the respiratory status through non-invasive support, fluid and electrolyte management, broad-spectrum antibiotics, and bronchodilators, a decision was made to observe the case further. The patient underwent upper gastrointestinal tract fluoroscopy and the gastroesophageal reflux extending to the mid-segment of the esophagus was detected. A cranial ultrasound raised suspicion for dysplasia of the corpus callosum, which was later confirmed by MRI showing thinning of the corpus callosum consistent with hypoplasia (**Figure 2**) for the patient's age. Multiple nodular lesions which are similar gray matter signals along the bilateral subependymal region evaluated as gray matter heterotopia (**Figure 2**). Additionally, a focal enlargement of cerebrospinal fluid (CSF) was also observed in the posterior fossa (**Figure 2**).

With these multisystemic imaging findings, the diagnosis of FLN-A mutation was suspected. In order to confirm the diagnosis, specific molecular testing for mutations of the FLN gene was performed and the final diagnosis was confirmed by the detection of duplicated heterozygous FLN-A mutation in our patient.

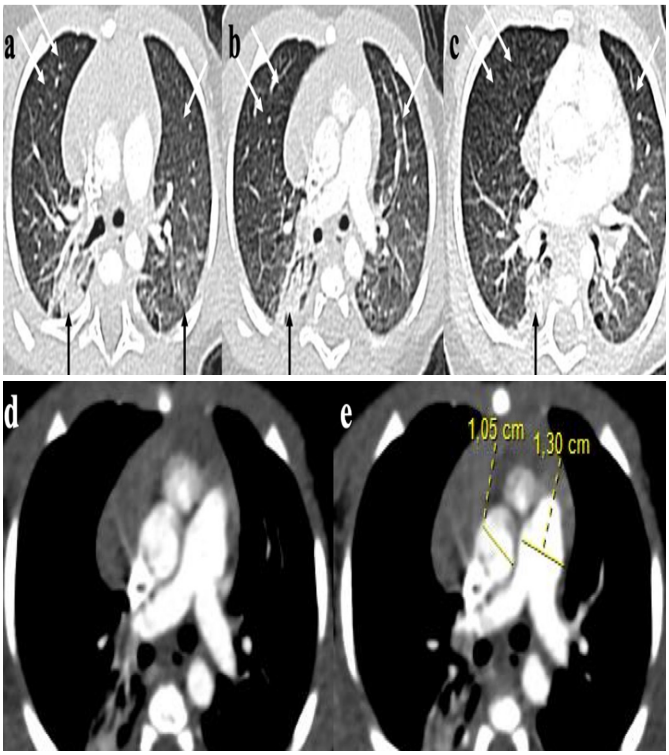

Figure 1a-e. Axial contrast-enhanced chest CT images demonstrate hyperinflation areas in the anterior segments of both lungs (**a, b,** and **c:** white arrows). Additionally, there is evidence of subsegmental atelectasis, and pleuroparenchymal fibrotic changes observed in the posterior segments of bilateral lungs (**a, b** and **c:** black arrow). A prominent finding is the increased ratio of main pulmonary artery (pulmonary trunk) to ascending aorta (**d, e**), which correlates with elevated pulmonary artery pressure, suggestive of pulmonary hypertension.

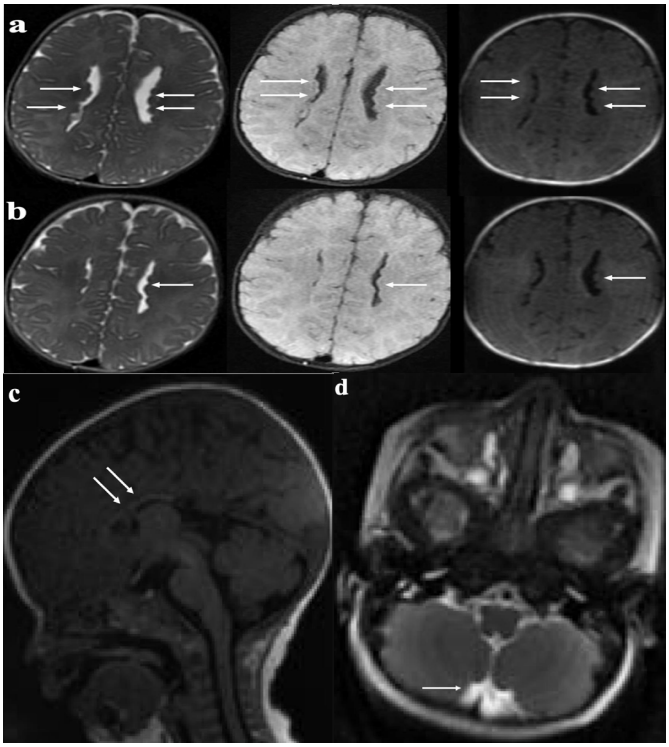

Figure 2a–d. The axial **(a, b)** T2-weighted, FLAIR, and T1-weighted turbo spin-echo (TSE) imaging reveals multiple nodules of heterotopia (arrows) gray matter remain isointense with the cortical gray matter lining along the body of lateral ventricles. Additionally, the sagittal 3D MPR image **(c)** demonstrates that a thinning of the corpus callosum according to age. Furthermore, there is a small focal cerebrospinal fluid (CSF) enlargement **(d)** at the posterior fossa

DISCUSSION

FLN-A is a ubiquitous phosphoprotein that links actin filaments and cytoskeleton to the plasma membrane. Moreover, being a structural component of the cytoskeleton, FLN-A has also been implicated in regulating many cellular signaling pathways and growth factors. The mutations in the FLN-A gene are associated with various multisystem abnormalities that affect all organs, including the brain, lungs, heart, bones, and skin.[1-3] The clinical heterogeneity of FLN-A mutations is extremely high as in our case.[13,15,16] Our case describes many specific and/or nonspecific radiological findings of multisystem involvement (periventricular heterotopia, corpus callosum hypoplasia, lung hyperinflation, pulmonary hypertension, and gastroesophageal reflux) and to our knowledge, FLN-A mutation associated multisystem involvement has not been reported radiologically before.

Macrothrombocytopenia is commonly shown in literature with FLN-A-associated periventricular heterotopia. It is thought that due to the premature fragile, immature platelets that have shorter life.[4] Our case had also decreased platelet counts with associated periventricular heterotopia, similar to the literature.

Multivalvular diseases have been commonly reported previously in the literature. Mitral valve disease affects 2-3% of the population and, as patients age, often requires corrective surgery. Myxomatous degeneration of the valves and regurgitation and prolapse of one or more of the aortic and mitral valves, sometimes with concomitant stenosis, have been seen frequently in boys. Females often have valve abnormalities, but most are asymptomatic. A smaller percentage of girls with familial valvular dystrophy develop mitral prolapse.[5,6] Bicuspid aortic valve (BAV) is the most frequent congenital heart disease, with an incidence of approximately 1%. It can be asymptomatic and associated with normal valve function. However, a series of complications, may develop valve incompetence to sudden death. The association of periventricular heterotopia with polivalvular disease and the BAV has been reported seldom in the literature as in our case.[17]

This rare entity may lead to chronic lung disease affecting mainly children (especially infant/toddler age group) and female individuals. It is part of the entities included in the childhood interstitial lung disease group of disorders and one of the etiologic factors of pulmonary hypertension. Recently, several pulmonary manifestations have been described including early respiratory failure, bronchopulmonary dysplasia, and imaging findings of pulmonary abnormalities were airway anomalies that included lung hyperinflation, lobar emphysema, and bronchial wall-thickening in association with interstitial changes such as peribronchial and interlobular septal thickening, ground glass opacification, severe lung airway cartilage deficiency, and abnormal elastic fibers in many studies.[6-8] Chest radiographs are still the mainstay of chest imaging. However, findings may be nonspecific and very subtle. CT helps to evaluate the major vessels and is superior to roentgenograms in many ways, detecting imaging findings that may be related to the underlying etiology; therefore, it is preferred despite the higher radiation risk. In our case, the patient presents with respiratory failure clinically and pulmonary hypertension on echocardiogram. The patient's chest CT findings were similar to previous studies, with hyperinflation in bilateral lung apical-anterior segments, atelectatic and pleuroparenchymal fibrotic changes in posterior segments, and vascular findings supporting pulmonary hypertension.

Due to the loss of FLN-A expression in intestinal smooth muscle, abnormal smooth muscle stratification may be seen during development, and this leads to decreased intestinal motility. Intestinal obstruction in the absence of a mechanical lesion is called congenital idiopathic intestinal pseudoobstruction. Patients variably present with decreased intestinal motility and a short, malrotated, and dilated small intestine, often with microcolon. This is often accompanied by failure to maintain body weight and growth and often leads to dependence on parenteral nutrition.[9] Gastroesophageal reflux disease is a clinical condition that affects millions of people worldwide and negatively impacts the quality of life. It is the involuntary retrograde passage of gastric contents into the esophagus with or without regurgitation and is considered a normal physiologic process, occurring daily in greater than one-third of all infants. However, it is accepted as a pathologic condition associated with poor weight gain, irritability, and dysphagia and often requires evaluation and treatment. Iqbal et al.[18] presented 4 cases and two of them had gastroesophageal reflux disease requiring Nissen and gastrostomy tube. Our patient also had gastroesophageal reflux accompanied by poor weight gain, suggesting that it was pathological. Even if gastroesophageal reflux is nonspecific, it may be useful to expand the manifestations of the disease.

PNH is a congenital brain malformation that is clinically diagnosed based on the imaging findings of heterotopic nodules composed of disorganized neurons along the lateral ventricles of the brain and often associated with epilepsy. The patients generally are of normal intelligence, although there have been associated findings of learning disabilities, namely, dyslexia. Parrini et al.[11] showed bilateral PNH, featuring contiguous heterotopic nodules, mega cisterna magna, cardiovascular malformations, and epilepsy that are associated with FLN-A mutations.[10,11] Pardoe et al.[19] specifically reported morphometric abnormalities in the corpus callosum in PNH and Lu et al.[2] described the corpus callosum in patients with PNH-associated epilepsy with FLNA mutation. We detected bilateral periventricular heterotopia, decreased caliber of corpus callosum evaluated as corpus callosum hypoplasia, and focal CSF enlargement in the posterior fossa, as described in the literature.

CONCLUSION

Mutation in the FLNA gene causes a wide spectrum of diseases including neuronal migration abnormality, and connective and vascular tissue anomalies notably interstitial lung diseases, pulmonary hypertension, myxomatous polyvalvular diseases, malformations of cortical development, periventricular heterotopia, migration anomalies, epilepsy, and decreased intestinal motility. Diseases associated with FLNA variants demonstrate considerable genetic and clinical heterogeneity. In this context, radiological findings are essential and invaluable for accurate diagnosis. Although many of these radiological findings may initially appear nonspecific and irrelevant, radiologists should keep imaging findings in mind and properly guide clinicians for comprehensive genetic evaluations. Such assessments aid in achieving prompt genetic diagnoses, which can significantly improve the patient's survival and social functionality in later life. Despite the rarity of this disorder and the relatively mild clinical presentation, this particular case presents an invaluable radiological perspective on multisystem involvement. It broadens our understanding of the spectrum of presentations associated with FLNA mutations and underscores the several imaging findings that clinicians should consider. These insights are essential for guiding advanced genetic investigations aimed at the early diagnosis of FLNA mutations.

ETHICAL DECLARATIONS

Informed Consent

The parents of patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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