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ORIGINAL PAPER

Combined cardiological and neurological abnormalities due to *filamin A* gene mutation

Marie Claire Y. de Wit · Irenaeus F. M. de Coo · Maarten H. Lequin · Dicky J. J. Halley · Jolien W. Roos-Hesselink · Grazia M. S. Mancini

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Abstract
Background Cardiac defects can be the presenting symptom in patients with mutations in the X-linked gene *FLNA*. Dysfunction of this gene is associated with cardiac abnormalities, especially in the left ventricular outflow tract, but can also cause a congenital malformation of the cerebral cortex. We noticed that some patients diagnosed at the neurogenetics clinic had first presented to a cardiologist, suggesting that earlier recognition may be possible if the diagnosis is suspected.
Methods and results From the Erasmus MC cerebral malformations database 24 patients were identified with cerebral bilateral periventricular nodular heterotopia (PNH) without other cerebral cortical malformations. In six of these patients, a pathogenic mutation in *FLNA* was present. In five a cardiac defect was also found in the outflow tract. Four had presented to a cardiologist before the cerebral abnormalities were diagnosed.
Conclusions The cardiological phenotype typically consists of aortic or mitral regurgitation, coarctation of the aorta or other left-sided cardiac malformations. Most patients in this category will not have a *FLNA* mutation, but the presence of neurological complaints, hyperlaxity of the skin or joints and/or a family history with similar cardiac or neurological problems in a possibly X-linked pattern may alert the clinician to the possibility of a *FLNA* mutation.

Keywords Filamin A · Outflow tract · Mitral valve · Neurology · Genetics · Aorta · Regurgitation · Nervous system · Congenital heart defects

M. C. Y. de Wit · I. F. M. de Coo
Department of Neurology, Erasmus MC, PO Box 2040, 3000 CA Rotterdam, The Netherlands

M. H. Lequin
Department of Radiology, Erasmus MC, PO Box 2040, 3000 CA Rotterdam, The Netherlands

D. J. J. Halley · G. M. S. Mancini (✉)
Department of Clinical Genetics, Erasmus MC, PO Box 2040, 3000 CA Rotterdam, The Netherlands
e-mail: g.mancini@erasmusmc.nl

J. W. Roos-Hesselink
Department of Cardiology, Erasmus MC, PO Box 2040, 3000 CA Rotterdam, The Netherlands

Introduction

Cardiac defects in adults are usually sporadic and rarely considered to be part of a hereditary syndrome. The presence of other congenital malformations or a positive family history should alert the clinician to the possibility of an underlying, possibly genetic cause [1, 2]. Combined neurological and cardiac disease is well recognized in neuromuscular disorders [3]. However, a cardiac defect can also be the presenting symptom in patients with a congenital malformation of the cerebral cortex due to mutations in the X-linked gene *FLNA* (OMIM 300017). Dysfunction of this gene leads to abnormalities in outflow tract development, often manifesting as a mitral or aortic valve insufficiency and a cerebral migration disorder, characterized by clusters of grey matter along the ventricles consisting of neurons that failed to migrate to the cortex during prenatal development [4]. Some mutations in *FLNA* can lead to craniofacial and skeletal abnormalities, including otopalatodigital (OPD) syndrome types 1 (OMIM 311300) and 2 (OMIM 304120), Melnick-Needles syndrome (MNS, OMIM 309350) and frontometaphyseal dysplasia (FMD, OMIM

305620). The filamin proteins (FLNA, FLNB and FLNC) are products of different genes and splice variants. Filamins stabilize F-actin networks in the cell and link them to cellular membranes by binding to transmembrane receptors or ion channels, thereby regulating cell morphology, membrane integrity and cell locomotion [5]. FLNA and FLNB are widely expressed, while FLNC is restricted to the striated muscle. Mutations in FLNC have been associated with myofibrillar myopathy [6]. FLNA is highly expressed in early myotubes, developing myofibrils and migratory neurons. During myofibril development FLNA is replaced by FLNB [5]. There seems to be some functional redundancy of both proteins [7]. Mutations in FLNB have only been described in skeletal chondrodysplasia, like Larsen syndrome (OMIM 150250), spondylocarpotarsal Dysostosis (OMIM 272460), atelosteogenesis I and III (OMIM 108720 and 108721) and boomerang dysplasia (OMIM 112310). Among these, only Larsen syndrome occasionally presents with cardiac outflow tract defects and none with cerebral periventricular nodular heterotopia (PNH). In this study, we evaluated patients known with a *FLNA* mutation for cardiac abnormalities.

Methods

We used our database of patients with malformations of cortical development to determine how often we see a combination of cerebral PNH and cardiac abnormalities due to *FLNA* mutations, to describe the patient characteristics and to provide information for the cardiologist as to when they should be alert to the possibility of an associated cerebral malformation. *FLNA* mutations were identified by direct sequencing of exons and intron exon boundaries (reference sequence NM_01110556.1).

Results

From our ongoing database of patients with malformations of cortical development, we identified 24 patients with bilateral PNH without other cerebral cortical malformations [8]. In six patients this was due to a pathogenic mutation in *FLNA*. Five of these *FLNA* patients had a cardiac defect in the outflow tract. Details of these five patients are found in the table and clinical descriptions below. Four presented to a cardiologist before the diagnosis of the cerebral abnormalities was known. In the 18 other patients with bilateral PNH without other cerebral malformations pathogenic mutations in *FLNA* were excluded, and none of these had a cardiac defect as evaluated by a cardiologist. Patients with other malformations of cortical development were not all screened by a cardiologist, so the incidence of cardiac defects in this group cannot be inferred from our data.

Clinical reports

Patient 1

The first patient is a boy (patient 1 in Table 1 and Figs. 1, 2), the third child of healthy parents of Somalian descent. A prenatal ultrasound at 20 weeks showed an unclassified cardiac abnormality. Pregnancy and term birth (38 weeks) were uncomplicated. Birth weight was 2,635 g, head circumference 34 cm (normal). Cardiac ultrasound and catheterization showed a cardiac malformation consisting of a situs solitus, AVVA concordant, mono-atrium, mitral atresia, hypoplastic left ventricle, double outlet right ventricle, patent arterial duct, severe hypoplasia of the transverse aortic arch and coarctation of the aorta. Physical exam showed a normal abdomen, cryptorchidism, a closed palate and normal facies, apart from minor anomalies of a preauricular pit on the left side and mildly posteriorly rotated ears. Neurological evaluation in the neonatal period showed an alert infant with normal movements, reflexes and muscle tone. EEG showed no epileptiform discharges. Brain MRI showed wide cerebral ventricles with bilateral PNH, a normal cortex, and a bifid septum pellucidum, and an enlarged retrocerebellar space with normal cerebellum

Table 1 Patient characteristics

Pt	Sex	Cardiological symptoms	Associated symptoms	Epilepsy	Outcome	Mutation *FLNA*
1	M	Mono-atrium, mitral atresia, hypoplastic LV, double outlet RV, aortic coarctation	–	–	Died age 2 m of heart failure	c.5290G>A
2	F	Aortic coarctation	Hyperlaxity skin and joints	–	Now 2 years old	c.220G>A
3	F	Severe aortic valve insufficiency	–	–	Died aged 71 years of subarachnoid hemorrhage	c.3045del5
4	F	Mild aortic valve stenosis and regurgitation	–	+	Now 46 years old	c.3582delC
5	F	Severe aortic valve regurgitation	–	–	Now 42 years old	c.6635delTCAG

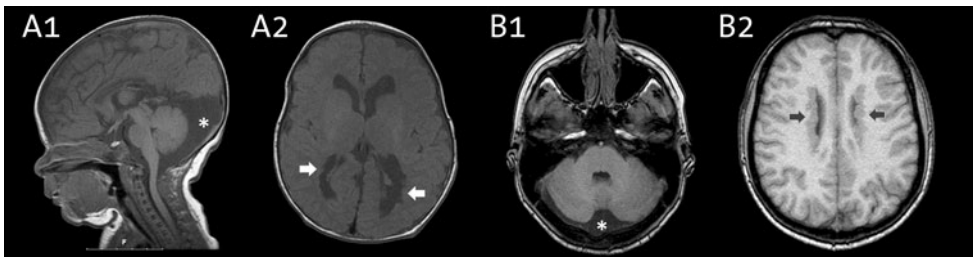

Fig. 1 Neuroimaging characteristics of a child (patient 2) in *A1* and *A2*, and an adult (patient 5) in *B1* and *B2*. All are T1 weighted MRI images. Note the periventricular nodular heterotopia (denoted by *arrows*) and the enlarged retrocerebellar space (denoted by a *star*)

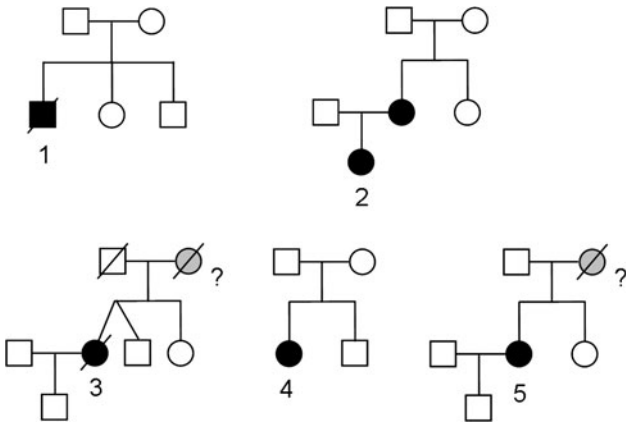

Fig. 2 Pedigrees of the described cases. FLNA mutation carriers in *black*, probably affected but deceased persons in *gray*. *Numbers* refer to the described cases

and brainstem. Thorax CT angiogram performed to classify the cardiac abnormality additionally showed incomplete fusion of the distal third part of the sternum. The patient died at the age of 2 months of heart failure. Autopsy was not allowed and the family was lost to follow-up.

FLNA sequencing of DNA extracted from leukocytes showed two sequence changes. The missense change c.5290G>A (p.A1764T) has been reported before in a woman with PNH and has been described as pathogenic, although there is no definitive evidence [4]. The second missense change was found in exon 20 (c.3035C>T) resulting in a serine to leucine substitution at position 1012 of the protein and has not been reported before in PNH or in the OPD-spectrum. This is a change in rod 1 (repeat 1–15) before the hinge 1 domain and is predicted to be a non-tolerated amino acid change in two different computer models. It is uncertain whether the second missense change contributes to the phenotype.

Patient 2

During the first pregnancy of a unrelated healthy Dutch couple prenatal ultrasound and prenatal MRI had shown a girl with a possibly enlarged heart and mildly enlarged cerebral ventricles (patient 2 in Table 1 and Fig. 2). Delivery at term (40.6 wks) was uncomplicated. Birthweight was 2,830 g and head circumference 37 cm (+2 SD). Postnatally, cardiac ultrasound showed a secundum atrial septal defect, coarctation of the aorta and mild aortic regurgitation. The coarctation was surgically corrected at the age of 16 days by resection and end-to-end anastomosis. She showed normal to mildly delayed cognitive development and delayed motor development with hypotonia and severe hyperlaxity. Facial features show a broad forehead, prominent orbital ridges, deep set eyes with down-slant, and a flat midface. She has never had seizures, and EEG showed no epileptiform discharges. Brain MRI showed bilateral PNH and an enlarged retrocerebellar cyst (Fig. 1). At the age of 3 months she developed dyspnoea due to congenital lobar emphysema of the right middle pulmonary lobe with bronchomalacia. She was successfully treated with a pulmonary lobectomy.

FLNA sequencing of DNA extracted from leukocytes showed a missense change c.220G>A in exon 2 (p.G74R). Family studies showed the mother, not the father, to be carrier of the same mutation. Cardiological evaluation, including ultrasound, of the mother was normal. The mother has hyperlaxity. Brain MRI of the mother showed bilateral PNH, typical of *FLNA* mutations. She subsequently developed epilepsy at age 27 years. This missense change was absent in leukocyte DNA of the maternal grandparents. These have no *FLNA* related complaints or symptoms, although brain MRI was not done. Its de novo occurrence in the family renders it very likely that c.220G>A, p.G74R is a pathogenic mutation.

Patient 3

A woman with a normal IQ and an otherwise unremarkable history underwent aortic valve replacement for severe aortic valve regurgitation at age 40 in 1975 (patient 3 in Table 1 and Fig. 2). Details on the pathology were lost. At age 55 she was diagnosed with heart failure and 1 year later she underwent heart transplantation. Macroscopic pathology showed a dilated heart and a dilated aortic root. The left ventricle shows subendocardial fibrosis. At age 60 she was diagnosed with severe venous varicosis of the legs and at age 70 an infrarenal aortic aneurysm with a 4.7 cm diameter was found and treated conservatively. She never had an epileptic seizure and showed no hyperlaxity of

joints or skin. At age 71 symptoms of mild cognitive decline prompted a brain CT showing bilateral PNH as a chance finding. Eight months later she died of a subarachnoid hemorrhage from a ruptured fusiform carotid aneurysm. Family history revealed that her mother had heart problems from a young age and died from heart failure at age 69, details could not be recovered. The patient had a healthy twin brother and a sister and a healthy son. The autopsy showed severe generalized atherosclerosis with mild dilatation of the thoracic aorta and an aneurysm of the abdominal aorta of 7 cm. Brain autopsy showed symmetrical bilateral PNH, and bilateral fusiform carotid aneurysms with widespread glomeruloid microvascular changes in the cerebral cortex [9].

Direct sequence analysis of the FLNA gene in DNA extracted from leukocytes showed a pathogenic frame shift mutation c.3045del5 in exon 21.

Patient 4

A 6-year-old girl presented with a cardiac murmur and was diagnosed with a mild aortic stenosis (9 mm gradient) and regurgitation with a normal left ventricle diameter that remained stable over the years (patient 4 in Table 1 and Fig. 2). She is now 46 years old and has a normal IQ. She had a first generalized epileptic seizure at age 28. Brain CT showed bilateral PNH. Dysmorphic evaluation showed no abnormalities and no hyperlaxity. She has no children and one healthy brother.

Direct sequence analysis of *FLNA* in DNA extracted from leukocytes showed a pathogenic frame shift mutation c.3582delC in exon 22.

Patient 5

A girl presented shortly after birth with cyanosis during feeding and was diagnosed with a ventricular septal defect and aortic regurgitation (patient 5 in Table 1 and Fig. 2). At age 24 the ventricular septal defect was surgically corrected and she received an aortic bioprosthesis. At age 36 years she underwent a Bentall procedure. At age 40, she presented to a neurologist because of a complicated migraine attack with aphasia. A brain MRI showed bilateral PNH and an enlarged retrocerebellar space (Fig. 1). Family history revealed that her mother died suddenly at age 57 from a rupture of the aorta. The patient has one sister with mild aortic regurgitation, she has been invited for counseling. The patient has a healthy son.

Direct sequence analysis of FLNA in DNA extracted from leukocytes showed a pathogenic mutation frame shift mutation c.6635delTCAG in exon 41.

Discussion

Five out of six patients with a pathogenic mutation in *FLNA* from our database show a combination of cardiac disease and bilateral cerebral PNH. Four patients presented to a cardiologist before or at the time of their neurological workup. Neurological signs were absent or mild at that time and the diagnosis of bilateral PNH was made later due to epileptic seizures (case 4), hypotonia (case 2) or during the workup of non-related complaints. This suggests that the cardiologist had the first opportunity to recognize these patients. Recently also X-linked mitral valvular dystrophy without neurological signs or symptoms of epilepsy was found to be caused by mutations in *FLNA*, however, brain imaging was not reported [10]. The cardiological phenotype is not always this specific. FLNA knock out mice show midline skeletal defects and early male lethality due to cardiac malformations in atrioventricular septal and outflow tract development [11]. Human patients also show abnormalities in the outflow tract ranging from patent ductus arteriosus, mitral or aortic valvular abnormalities to coarctation of the aorta, and ascending aorta aneurysm [12–14]. Cerebral PNH in *FLNA* patients is caused by impaired migration of later born neurons due to disrupted cell adhesion and abnormal ventricular ependymal function [15]. This shows that pathways involved in cell adhesion can both affect the neuro-epithelium and vascular development. Apart from cerebral and cardiovascular developmental defects *FLNA* mutations can also cause connective tissue abnormalities, and autopsy studies show abnormal glomeruloid microvascular proliferations in the brain [9, 15]. A combination of PNH and Ehlers-Danlos syndrome with joint hyperlaxity and aorta aneurysms caused by a mutation in *FLNA* has been described in females [16]. Neurological phenotypes associated with PNH are diverse and range from epilepsy and normal development to patients with multiple congenital anomalies and mental retardation. In males mutations are often prenatal lethal. Less severe mutations with residual filamin A function are found in males with PNH. One male patient has been described with PNH and a lethal complex cardiac malformation, including atrial and ventricular septal defect and persistent left superior caval vein [12]. Interestingly, gain of function mutations of FLNA are associated with syndromes with craniofacial and skeletal abnormalities, including otopalatodigital syndrome types 1 and 2, Melnick-Needles syndrome (MNS) and frontometaphyseal dysplasia [17]. In these syndromes several male patients have been described with heart defects, cryptorchidism and umbilical hernia, but no PNH [17]. The combination of mitral and/or aortic regurgitation and skeletal abnormalities with hyperlaxity is also found in autosomal dominant Marfan syndrome (OMIM 154700), in the allelic Shprintzen-Goldberg

syndrome (OMIM 182212) and in Loeys-Dietz syndrome type 1A and B (OMIM 609192 and 610168). Some neuromuscular abnormalities are described in these patients, but no cerebral cortical developmental abnormalities.

Although we did not find any cases, cardiac defects are reported to be associated with some other cerebral PNH phenotypes. Patients with Williams syndrome, caused by a microdeletion of chromosome 7q11.22-23, have distinctive facial dysmorphias, 'elfin face', and often cardiac defects, such as supravalvular aortic stenosis, mitral or pulmonary valve abnormalities, and atrial or ventricular septum defect. One case has been described with associated PNH [18]. In chromosome 6q terminal deletion syndrome, brain MRI commonly shows hypoplasia of the corpus callosum, and a few patients have been described with associated PNH [19]. About half of 6q terminal deletion patients are reported to have cardiac abnormalities, primarily ventricular or atrial septum defect. Distal duplications of chromosome 5p have been associated with PNH in two patients, one of which also had atrial septum defect and mitral and tricuspid valve prolapse [20]. Genetic factors related to similar cardiac malformations without PNH are being widely investigated, but still only few genes are known to cause a developmental defect of the atrioventricular septum and the outflow tract in humans [21–23].

Conclusion

Patients with mutations in *FLNA* show a cardiological phenotype with aortic or mitral regurgitation, coarctation of the aorta or other left-sided malformations. Although patients with cardiac defects in this category are numerous and most will not have a *FLNA* mutation, the presence of neurological complaints, hyperlaxity of the skin or joints and/or a family history with similar cardiac or neurological problems in a possibly X-linked pattern should alert the clinician to the possibility of a *FLNA* mutation. Recognition will enable genetic testing and genetic counseling for patients and their family.

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Conflict of interest None.

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