Isolated Dislocation of Ocular Lens

Gabriela Acucella1, Enrico Finale2*, Gaetano Auletta3, Andrea Guala1

1Department of Pediatrics and Neonatology, Castelli Hospital, Verbania, Italy
2Department of Obstetrics and Gynecology, Castelli Hospital, Verbania, Italy
3University of Eastern Piedmont, Novara, Italy
*Corresponding author: enrico.finale@gmail.com

Abstract We describe a case of a child with isolated dislocated of ocular lens, due to mutation in FBN1 gene. Differential syndromic diagnosis is made and we discuss to importance of clinical follow-up to exclude/confirm cardiologic complications due to Marfan syndrome.

Keywords: Ectopia lentis, Fibrillin 1 gene, Marfan syndrome


1. Case Report

We describe the case of a child 3 years old came to our attention for a dislocated higher bilateral lens that was diagnosed during an eye screening. The initial medical history was negative for major malformations, hereditary diseases and early onset mental delay, cancer recurring and for parents consanguinity. The child is an only child born to vaginal birth and she never showed pathologies. The examination highlights a height to 90th percentile while the weight and the head circumference are to 50th. The child has not dysmorphics except the very arched palate and valgus knee.

2. Differential Diagnosis

The presence of lens dislocation diagnosis oriented the team to research new signs and symptoms related to the main syndromes associated with lens dislocation, such as: Marfan syndrome, Weill-Marchesani syndrome, Ehler-Danlos syndrom and homocystinuria. The clinical examination had ruled out the Weill-Marchesani and Ehler-Danlos syndromes because were not present in the child, short stature, brachydactyly, microspherophakia (Weill-Marchesani), and not even also laxity and thinness of the skin, ligament hyperlaxity (Ehler-Danlos). A cardiologist advise and an echocardiogram allowed us to exclude the mitral valve prolapse and/or aortic arch dilatation. We counseled to do an hands radiography to study the metacarpophalangeal profile and homocysteinemia dosage, results were normal. We excluded the Marfan syndrome since were not present Ghent criterions.

The most likely hypothesis seemed to be the isolated congenital dislocation of the lens (Table 1 differential diagnosis) was necessary to do a molecular investigation to establish if was a lectopia lentis 1 (OMIM 129600), dominant autosomal condition due to the mutation of the gene FBN1 or ectopia lentis 2 (OMIM 225100), recessive autosomal condition due to the mutation of the gene ADAMTSL4. The diagnosis has been made thanks to the molecular investigation of the fibrillin gene 1 (sequencing FBN1). The used methodology was the DNA extraction from peripheral blood and amplification of the 65 exons of the gene FBN1 through PCR, analysis on DHPLC, Direct automatic sequence and sequence analysis with software "sequencer 3.0". The analysi of the 65 coding regions and relatives flanking regions inclusive of the canonical sites of "splicing" of the gene FBN1 showed the presence of exon 1 of a missense mutation in Hetrozygosity.

3. Discussion

The ectopia lentis is a hereditary disorder of the connective tissue with predominating of 1/100.000, in most cases it is transmitted like an autosomal dominant trait although there are rare cases with recessive autosomal [1,2] and not rare new mutations. The ectopia lentis refers a dislocation of lents from his normal position; in this condition the zonular filaments and the suspensory ligaments are alongated or discontinuous. Very often ectopia lentis is a manifestation of systemic diseases and in particular is associated to Marfan syndrome [3]. The ectopia lentis rappresents one of the major criteria for the diagnosis of Marfan syndrome although the ectopia lentis is present only in 60% of cases of suffering people [4].

The Marfan syndrome is a disorder of the connective tissue with autosomal dominant inheritance and its incidence is about 2 cases per 10.000 individuals [5], with a prevalence of 2-3 cases out of 10.000 [5,6,7], without different incidence about sex, race, or geographical distribution. The disorder is caused by mutations of the gene FBN1, the protein constitutes the microfibrils of elastic fibers.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptom overlap with Marfan Syndrome</th>
<th>Discriminating features</th>
<th>Discriminating Features</th>
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<tbody>
<tr>
<td>Loeys-Dietz Syndrome</td>
<td>- Aortic root enlargement and dissection&lt;br&gt;- Variable skeletal findings&lt;br&gt;- Dural ectasia&lt;br&gt;- Streach Marks</td>
<td>- Craniosynostosis&lt;br&gt;- Diffuse aortic and arterial aneurysms and dissections&lt;br&gt;- Arterial tortuosity&lt;br&gt;- Gastrointestinal problems&lt;br&gt;- Cleft palate/ bifid uvula&lt;br&gt;- Club foot&lt;br&gt;- Cervical spine instability&lt;br&gt;- Hypertelorism&lt;br&gt;- Thin and velvety skin&lt;br&gt;- Easy bruising&lt;br&gt;- Translucent skin&lt;br&gt;- Dystrophic scars</td>
<td>TGFBR1 TGFBR2</td>
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<tr>
<td>Familial Thoracic Aortic Aneurysm and Dissection (FTAAD)</td>
<td>- Aortic enlargement and dissection</td>
<td>- Lack of marfanoid skeletal features&lt;br&gt;- Iris flocculi&lt;br&gt;- Levido reticularis&lt;br&gt;- Dislocated lens and dural ectasia not found</td>
<td>ACTA2 MYLK PRKG1</td>
</tr>
<tr>
<td>FTAAD with bicuspid aortic valve (BAV)</td>
<td>- Aortic enlargement (root and ascending) and dissection</td>
<td>- Male predominance&lt;br&gt;- Aortic stenosis can occur</td>
<td>Unknown</td>
</tr>
<tr>
<td>FTAAD with patent ductus arteriosus (PDA)</td>
<td>- Aortic enlargement and dissection</td>
<td>- Frequent PDA</td>
<td>MYH11</td>
</tr>
<tr>
<td>Arterial tortuosity syndrome (ATS)</td>
<td>- Aortic enlargement and dissection</td>
<td>- Generalized arterial tortuosity&lt;br&gt;- Arterial stenosis&lt;br&gt;- Facial dysmorphism</td>
<td>SLC2A10</td>
</tr>
<tr>
<td>Ectopia lentis syndrome (dislocated lens)</td>
<td>- Eye lens dislocation&lt;br&gt;- Common skeletal findings</td>
<td>- Aortic root dilation/aneurysms not found</td>
<td>FBN-1 LTBP2 ADAMTS-L-4</td>
</tr>
<tr>
<td>Shprintzen-Goldberg syndrome</td>
<td>- Mitral valve prolapse&lt;br&gt;-Skeletal findings&lt;br&gt;- Myopia</td>
<td>- Craniosynostosis&lt;br&gt;- Hypertelorism&lt;br&gt;- Delayed motor and cognitive milestones&lt;br&gt;- Mental retardation&lt;br&gt;- Aortic root dilatation is uncommon&lt;br&gt;- C1-C2 abnormality</td>
<td>SKI (rarely FNB-1)</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome</td>
<td>- Skeletal findings&lt;br&gt;- Valve prolapse and Aortic enlargement and dissection in selected types only</td>
<td>Vascular type:&lt;br&gt;- Arterial, intestinal, uterine fragility and rupture&lt;br&gt;- Characteristic facial appearance (thin lips and philtrum, small chin, thin nose, and large eyes&lt;br&gt;- Thin translucent skin with easy bruising&lt;br&gt;- Dystrophic scars&lt;br&gt;-Facial characteristics&lt;br&gt;- Joint subluxation common&lt;br&gt;- Skin soft or velvety, may be mildly hyperextensible&lt;br&gt;Hypermobility Type:&lt;br&gt;- Progressive scoliosis present at birth or within first year of life&lt;br&gt;- Scleral fragility and rupture of the globe&lt;br&gt;- Severe muscle hypotonia at birth&lt;br&gt;- Friable, hyperextensible skin&lt;br&gt;- Generalized joint laxity&lt;br&gt;Classic type:&lt;br&gt;- Skin fragility and hyperextensible&lt;br&gt;- Widened atrophic scars&lt;br&gt;- Joint hypermobility&lt;br&gt;- Aortic root dilatation can occur</td>
<td>COL3A1 (vascular)&lt;br&gt;COL9A1 (hypermobility)&lt;br&gt;COL9A2&lt;br&gt;COL5A1/COL5A2 (classic)&lt;br&gt;COL11A1/COL11A2&lt;br&gt;COL11A2</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>- Mitral valve prolapse&lt;br&gt;- Eye lens dislocation and myopia&lt;br&gt;- Skeletal findings</td>
<td>- Arterial and venous thrombosis&lt;br&gt;- Mental retardation&lt;br&gt;- Seizures common</td>
<td>CBS</td>
</tr>
<tr>
<td>Beals syndrome (congenital contractural arachnodactyly)</td>
<td>- Mitral valve prolapse and enlargement can occur&lt;br&gt;- Variable skeletal findings</td>
<td>- Crumpled appearance to the top of the ear&lt;br&gt;- Inability to fully extend multiple joints such as fingers, elbows, knees, toes and hip contractures&lt;br&gt;- Delay in motor development often occurs (due to congenital contractures)&lt;br&gt;- Eyes are not affected&lt;br&gt;- Dissections are very rare</td>
<td>FBN-2</td>
</tr>
<tr>
<td>Stickler syndrome</td>
<td>- Myopia&lt;br&gt;- Retinal detachment joint hypermobility or contracture&lt;br&gt;- Scoliosis&lt;br&gt;- Mitral valve prolapse</td>
<td>- Hearing loss&lt;br&gt;-Choriorretinal and vitreous degeneration are the hallmark of the syndrome&lt;br&gt;- Orofacial involvement such as cleft palate&lt;br&gt;- Premature osteoarthritis</td>
<td>COL2A1 COL9A1 COL9A2 COL11A1 COL11A2</td>
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<td>MASS phenotype</td>
<td>- Mitral valve prolapse&lt;br&gt;- Aorta root diameter at the upper limits of normal&lt;br&gt;- Skin (streach marks)&lt;br&gt;- Skeletal features (scoliosis, chest wall deformities, joint hypermobility)</td>
<td>- Aorta does not progress in enlargement&lt;br&gt;- Dislocated lenses not found</td>
<td>FBN-1 (rarely)</td>
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**Table 1. Differential diagnosis (adapted from The Marfan Foundation)**
The main features of the Marfan syndrome involving the cardiovascular, skeletal, and visual systems; can be involved also cutaneous system, respiratory and nervous [8]. The Marfan syndrome diagnosis is posed according to the Ghent criteria, which included different manifestations, including in particular: lens dislocation, art proximal aneurysm and an excessive growth of long bones [9]. According to Ghent criteria (Table 2) for the clinical diagnosis of the Marfan syndrome required a major criteria in two organs/systems and the involvement of a third organ/system. In familial cases are sufficient the presence of major criteria in one organ/system and the involvement of a second organ/system. In adults the diagnosis of Marfan syndrome, in the context of the classical multisystem involvement, is relatively simple. In children can be problematic to have the diagnosis because many manifestations are age-dependent [10]. While the ectopia lentis is a relatively moderate impairment where an early diagnosis and a careful ocular follow-up can avoid the blindness risk. The morbidity and mortality of Marfan Syndrome are mainly related to cardiovascular manifestations like dissections/aortic aneurysms and arrhythmias which can cause sudden death in young people.

<table>
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<th>Table 2. Ghent nosology 2010</th>
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<tbody>
<tr>
<td>In assenza di storia familiare</td>
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<tr>
<td>Ao (Z&gt;2) e EL = MFS*</td>
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<tr>
<td>Ao (Z&gt;2) e FBN1 = MFS*</td>
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<tr>
<td>Ao (Z&gt;2) e systematic score = MFS</td>
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<tr>
<td>EL e FBN1 con nota Ao =MFS</td>
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<tr>
<td>Ao = Aorta; EL = Ectopia Lentis; FH = Family History; MFS = Marfan Syndrome</td>
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</tbody>
</table>

* consider the differential diagnosis with related pathologies.

After the revision of Ghent Criteria in 2010 [11] many patients who previously received a diagnosis of an isolated ectopia lentis, they were reclassified and they received a diagnosis of Marfan syndrome with important implications of clinical and instrumental follow-up [12].

4. Conclusions

The primary objective in patients with a diagnosis of ectopia lentis 1 is to excluded in time the reclassification of disease in Marfan syndrome. The international guidelines recommend the use of a validated systematic score that is based on the familia response of the disease, ascending aortic ectasia and of the lens luxation, which offers to the other clinical characteristics a different score according to their specificity for the syndrome [11].

The follow-up will have to identify early the presence of the aortic bulb dilation by an echocardiography with the application of international nomograms and calculating the ratio area bulb/height; identification and evaluation of mitral valve disease and a possible degree of valvular insufficiency associated; evaluation of the lens position and the possible degree of myopia; identification of a possible family history (certainty relative affected or carrier of mutation already identified); systemic score calculation (Table 3) considering that a score ≥7 gives the diagnosis of Marfan syndrome.

<table>
<thead>
<tr>
<th>Table 3. Systematic score (adapted from The Marfan Foundation)</th>
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<tr>
<td>FEATURE</td>
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<tr>
<td>Wrist AND thumb sign</td>
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<tr>
<td>Wrist OR thumb sign</td>
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<tr>
<td>Pectus carinatum deformity</td>
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<tr>
<td>Pectus excavatum or chest asymmetry</td>
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<td>Hindfoot deformity</td>
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<tr>
<td>Plain flat foot (pes planus)</td>
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<tr>
<td>Pneumothorax</td>
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<tr>
<td>Dural ectasia</td>
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<tr>
<td>Protrusio acetabulae</td>
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<tr>
<td>Reduced upper segment/lower segment AND increased arm span/heath ratios</td>
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<tr>
<td>Scoliosis or thoracolumbar kyphosis</td>
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<tr>
<td>Reduced elbow extension</td>
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<tr>
<td>3 of 5 facial features</td>
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<tr>
<td>Skin striae</td>
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<tr>
<td>Myopia</td>
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<td>Mitral valve prolapse</td>
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<td>Total ≥ 7 = Marfan syndrome</td>
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</table>

References


