Russian Family with X-linked Alport Syndrome and Cardiovascular Abnormalities

Groznova Olga1,*, Shentseva Darya2, Shagam Lev3, Sukhorukov Vladimir.3, Dlin Vladimir2

1Cardiovascular system pathology department, Research and Clinical Institute for Pediatrics at Pirogov Russian National Research Medical University, Moscow, Russia
2Nephrology department, Research and Clinical Institute for Pediatrics at Pirogov Russian National Research Medical University, Moscow, Russia
3Laboratory department, Research and Clinical Institute for Pediatrics at Pirogov Russian National Research Medical University, Moscow, Russia

*Corresponding author: ogroznova@gmail.com, ogroznova@pedklin.ru

Received May 18, 2015; Revised May 26, 2015; Accepted June 03, 2015

Abstract Background: Alport syndrome (AS) is an inherited disease. Clinical findings usually include hematuria, proteinuria and arterial hypertension. Hearing loss and ocular abnormalities are common symptoms. In the last years there are some clinical observations of arterial disease (aortic aneurysm, aortic dissection) in males with AS.

Methods: coding exons and splice sites of the abovementioned genes were sequenced in on Ion Torrent platform. Detailed clinical examination was obtained. Ophthalmologic and otologic evaluations, pure tone audiometry, electrocardiography, ECHO-cardiography, 24-hour blood pressure monitoring and retroperitoneal ultrasonography were performed.

Results: a novel dominant missense mutation c.G3098A, p.1033 G>D in the collagen type IV alpha-5 gene (COL4A5) was revealed in five family members. New aspects of phenotype evaluated: cardiovascular abnormalities (asymptomatic aortic enlargement, left ventricular dilatation, aortic insufficiency); early childhood onset of systemic hypertension; absents of ocular abnormalities. Microhematuria, proteinuria (in progress up to 2.0 g/l) and early childhood onset of systemic hypertension are discussed as a result of heterozygous COL4A5 mutations in affected females.

Conclusions: molecular genetics help to understand variable clinical phenotypes of AS patients. New findings about cardiovascular abnormalities should stimulate doctors to make cardiology examination in all affected subjects.

Keywords: alport syndrome, phenotype, heart, arterial diseases, valves, hypertension, cardiovascular


1. Introduction

Alport syndrome (AS) is an inherited disease. Approximately 85% of cases - are the results of X-linked COL4A5 mutations on chromosome Xq22.3, expressed in the glomerular basement membranes and are responsible for membrane structural abnormalities and chronic renal failure, that may lead to end-stage kidney disease (ESKD) in the third decade of life. AS affects 1 of 50,000 live births [1]. Clinical findings usually include continuous microscopic hematuria, episodes of macroscopic hematuria, proteinuria and arterial hypertension. Hearing loss and ocular abnormalities are common symptoms.

Now days hundreds of pathogenic variants in the COL4A5 gene have been described [2]. The identification of COL4A5 mutations in patients with AS should be a routine diagnostic test, because it helps to categorize variants of syndrome for pathogenicity. DNA variant database of AS that’s made with standardized nomenclature may clarify clinical symptoms of disease, assess the prognosis of the disease, improve genetic counseling and phenotype prediction in patients. Exact identifying of genotype in an affected person may avoid renal biopsy for the diagnosis in some group of patients. So identification of a novel mutation and evaluation of new genotype-phenotype correlations is important.

Cardiovascular abnormalities

Some genetic syndromes are known to occur in association with aortic aneurysms (for example Marfan syndrome). In the last years there are some clinical observations of arterial disease (aortic aneurysm, aortic dissection) in males with AS [3,4,5]. Till now days arterial disease was an unusual clinical feature of AS. Severe vascular complications in males with AS are not common. Subclinical symptoms of cardiovascular abnormalities are not well understood. There is a suggestion, that type IV collagen of α5(IV) and α6(IV) chains may play a role in maintaining of aorta vascular integrity. Systemic arterial hypertension (quite usual for AS patients) secondary to chronic kidney disease can also be a factor for aortic aneurysm in young patients [6]. So association between AS and aortic disease is not clearly understood. The time
of arterial disease onset in patients with AS is not clear. Clinical significance of aortic aneurysm and dissection is important in any patient. Total ECHO screening and MRI of aortic abnormalities in patients with AS will be proved after clear understanding of cardiovascular abnormalities role in pathogenesis of this disease.

2. Materials and Methods

We review the clinical data of AS in a Russian family with five affected members and one healthy control from the same family. X-linked inheritance was suggestive (Figure 1). Genomic DNA was extracted and the coding exons and splice sites of the abovementioned genes were sequenced in on Ion Torrent platform.

For each affected individual a detailed clinical examination with routine blood and urine tests was obtained. Ophthalmologic and otologic evaluations, pure tone audiometry, electrocardiography, ECHO-cardiography, 24-hour blood pressure monitoring and retroperitoneal ultrasonography were performed.

Fig. 1. Russian family with Alport syndrome

I1: early age of onset, neurosensory hearing loss, died with the diagnosis of end stage kidney disease;
I2: age of onset unknown, continuous hematuria 100 cells/ml, proteinuria up to 2 g/l, glomerular filtration rate (GFR) 78 ml/min, systemic hypertension;
II1: age of onset 3 years old, continuous hematuria 100 cells/ml, proteinuria up to 2,5 g/l, GFR 82 ml/min;
II2: age of onset before 1 year old, continuous hematuria 280 cells/ml, proteinuria up to 0,1 g/l, GFR 88 ml/min, systemic hypertension, neurosensory hearing loss;
III1: age of onset before 1 year old, continuous hematuria 380 cells/ml, proteinuria up to 0,3 g/l, GFR 107 ml/min, systemic hypertension.

3. Results

A novel dominant missense mutation c.3098G>A, p.G1033D in the collagen type IV alpha-5 gene (COL4A5) causes X-linked AS in this Russian family was revealed in all family members affected.

Male patient demonstrated early onset of hematuria, proteinuria, neurosensory hearing loss and cardiovascular abnormalities; all affected females present in childhood with continuous microscopic hematuria, proteinuria and episodes of macroscopic hematuria. Episodes of macroscopic hematuria were associated with upper respiratory tract infections and other causes. Hematuria characterized by early-onset (before 1 year of age). Proteinuria in this family started remarkably earlier than expected from other publications [7] – not in adolescence but in early childhood in affected persons.

Glomerular filtration rate was low in affected male – 50 ml/min. All but one affected female demonstrated slightly abnormal glomerular filtration rate: in a 63 year old woman - 78 ml/min, in a 29 year old woman - 82 ml/min, in a 5 year old girl - 88 ml/min. The youngest affected girl (3 years old) has normal glomerular filtration rate - 107 ml/min.

None of the affected individuals with this mutation demonstrate any ocular abnormalities (even in the peripheral retina). The new fact is that systemic hypertension was found in female carriers in early childhood: a 3 year old girl was admitted to our department with systemic hypertension and a history of microscopic hematuria. The family history was remarkable for the presence of two other female carriers (grandmother 63 year old and a 5 year old girl) with similar health concerns. A 29 year old affected female has no systemic hypertension. Microscopic hematuria in the 29 and 63 year old female-carriers was not increased by age. Proteinuria in these two affected females has had gradual progression up to 2,0 g/l.
Two males affected (a 26 year old man and one man died at 33 years old; DNA of deceased patient was not examined) demonstrated early onset of renal abnormalities followed by end stage kidney disease (ESKD) in the 4-th decade of life in deceased person. The 33 years old affected male died with the diagnosis of ESKD before molecular genetic diagnostic was possible and before renal transplantation. Neurosensory hearing loss was presented in all affected males.

Marfan-like features were not found in this family phenotype.

**Cardiovascular Abnormalities**

In this family cardiovascular examination evaluated asymptomatic aortic annular, aortic sinuses and ascending aorta enlargement, mildly abnormal left anterior ventricular end diastolic diameter, aortic insufficiency (moderate and mild) and systemic hypertension. All affected patients have enlargement of aortic diameter on annular level. Elder patients (63, 29 and 26 years old) have enlargement of aortic diameter on Valsalva sinuses level. The male patient and the female 63 year old demonstrated enlargement of ascending aorta (Table 1). Mildly abnormal left ventricular end diastolic diameter was evaluated in the male patient. Left ventricular dilatation is suspected to be associated with the presence of aortic regurgitation. Aortic insufficiency (moderate) was observed in the male patient and the 63 year old female, mild aortic insufficiency – in the other 3 affected family members. Contractility of the left ventricular was normal in all family members. Systemic hypertension was identified in all but one (a 29 year old woman) affected patients. In two young girls is was firstly evaluated systolic and diastolic arterial hypertension mostly at night time, in the affected male and 63 years old female – stable systemic hypertension was diagnosed in the second decade of life and supposed to be secondary to chronic kidney disease. Both of patients have treatment with angiotensin converting enzyme inhibitor and calcium blocker.

<table>
<thead>
<tr>
<th>Case (see Figure 1)</th>
<th>I²</th>
<th>II²</th>
<th>II¹</th>
<th>III¹</th>
<th>III²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63</td>
<td>29</td>
<td>26</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Body surface area (BSA) m²</td>
<td>1,80</td>
<td>1,59</td>
<td>1,89</td>
<td>0,81</td>
<td>0,71</td>
</tr>
<tr>
<td>Aortic diameter (annular level), cm/Z-score*</td>
<td>28,3/29</td>
<td>24,2/2,46</td>
<td>30,6/3,6</td>
<td>18,2/3,23</td>
<td>17,7/3,51</td>
</tr>
<tr>
<td>Aortic diameter (Valsalva sinuses level), cm/Z-score*</td>
<td>4,1/3,99</td>
<td>3,0/1,71</td>
<td>3,85/2,98</td>
<td>1,9/-0,15</td>
<td>2,0/0,932</td>
</tr>
<tr>
<td>Ascending aorta diameter, cm/Z-score*</td>
<td>3,85/5,27</td>
<td>2,46/1,19</td>
<td>3,17/2,72</td>
<td>15,2/-0,14</td>
<td>15,6/0,76</td>
</tr>
<tr>
<td>Left ventricular end diastolic diameter, cm/Z-score*</td>
<td>5,48/0,88</td>
<td>5,1/3,20</td>
<td>6,3/1,75</td>
<td>3,8/0,111</td>
<td>3,5/-0,115</td>
</tr>
<tr>
<td>Aortic valve insufficiency (grade)</td>
<td>moderate</td>
<td>mild</td>
<td>moderate</td>
<td>mild</td>
<td>mild</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* normal range for Z-score: from -1,65 up to 1,65. (For aortic root in Marfan syndrome patients normal range for Z-score from -2,0 up to 2,0).

**4. Discussion**

The new concept of continuous phenotypic spectrum in patients with AS is described recently [7]. Phenotype variation from classical AS, characterized by early ESKD, ocular defects and neurosensory deafness, moving to milder cases and ending through some subclinical forms of disease is proved in many patients. A large amount of genetically proven X-linked AS descriptions allows us to understand variability of the AS phenotype more clearly.

The new idea of our publication is that the connective tissue abnormalities in the heart of patients with AS seems to be more global, than we thought before. It may be a combination of arterial disease caused by collagen structural abnormalities and secondary complications. It occurs in affected males and females at an early age. Clinically significant symptoms manifestation (aortic dissection) was described in literature only in some affected males. This problem requires further research.

The aortic valve annular enlargement and valve insufficiency evaluated in all affected persons seems to be remarkable. In all elder patients Valsalva sinuses enlargement is present. The male patient and the female 63 year old have enlargement of aortic aorta. We suppose collagen abnormalities stimulate this process. Valve insufficiency increases the blood volume in left heart chambers and provokes dilatation of left ventricle. This secondary process may stimulate aortic root dilatation in the presence of collagen abnormalities. We need more information about the early stages of cardiovascular abnormalities in patients with X-linked AS. Routine ECHO is seemed to be a gold standard of affected person examination in AS. In some patients it may be completed by MRI.

In females affected we demonstrate the early onset of systemic hypertension (3 and 5 years old girls) evaluated by 24-hour blood pressure monitoring, early onset (age of 3 years) and high progression of proteinuria up to 2,0 g/l in 29 and 63 years old affected females.

Notable in the family with this new mutation is an absence of any ocular abnormalities.

All affected females in this family have had no symptoms of kidney disease since the latter were subclinical. The family was ignorant about the systemic hypertension in the young girls. They failed to make urine laboratory tests or cardiovascular examination for these girls before the diagnosis of AS was confirmed in one male member of the family. The 29 year old affected female did not pay attention on “some” abnormalities in routine urine examinations before the affected male was evaluated in the family.

Demonstration of this family with four females affected support Savige J. et all, presumed that affected mothers of males with X-linked AS may be discouraged from renal donation because of their own risk of kidney failure [8]. Our demonstration may add affected sisters and other
affected female relatives to this group. Thorough examination is needed in all females in affected families.

5. Conclusion

A novel dominant missense mutation c.G3098A, p.1033 G>D in the collagen type IV alpha-5 gene causes X-linked AS in the Russian family with one affected male and four affected females was revealed. New phenotype findings were: cardiovascular abnormalities (asymptomatic aortic root enlargement, aortic valves insufficiency (mild and moderate) in all affected members, early onset of systemic hypertension in one male and three females; early onset (before 3 years of age) and progression of proteinuria up to 2.0 g/l in affected females; absents of any ocular abnormalities. In summary of the data, cardiovascular abnormalities may be a new symptom of AS. New findings about cardiovascular abnormalities in AS should stimulate doctors to make cardiology examination in all affected subjects.

References