AORTIC DISORDERS, FACIAL DYSMORPHISM AND MENTAL RETARDATION: CLINICAL FEATURES AND GENETIC CONDITIONS

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ABSTRACT

***Objectives**: The aim of the present article is to describe the clinical features and genetic conditions of the clinical syndromes/association characterized by facial dysmorphism, mental retardation, and aortic dilation, and compare with those of the syndromes with facial dysmorphism, mental retardation, and aortic stenosis.*

***Methods**: International literature of the syndromes characterized by facial dysmorphism, mental retardation and aortic dilation/stenosis published between 1980 and 2012 have been comprehensively retrieved. The clinical and genetic conditions were compared among different syndromes.*

***Results**: Aortic dilation in association with the facial changes and mental retardation suggested a Marfan-related connective tissue disorder in these patients who might have FBN1, FBN2, TβRI and TβRII gene mutations. Syndromes with facial dysmorphism, mental retardation and aortic stenosis prevail with chromosomal mutations and the patient's typical clinical features like more slant eye fissures, short statue and sometimes mild intellectual disability. In this way, information in regard to the differential diagnoses is to be clarified.*

***Conclusion**: The association of facial dysmorphism and mental retardation, in particular in children, may lead us to the diagnostic consideration of an aortic disorder. The dilated aorta, in this association, may mean a weak aortic wall caused by connective tissue fragility, due to mutational disorders of specific genes, including TGF-β signaling or X chromosome genes. Whereas, the aortic stenosis when associated with facial dysmorphism and mental retardation implicate alternative genetic malformations, such as chromosomal mutation or microdeletion.*

***Key words**: Aorta, connective tissue diseases, facial dysmorphism, mental retardation, rare diseases.*

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Introduction

Cardiovascular malformations subjected to genetic mutations may affect the cardiovascular systems, resulting in congenital heart defects, cardiomyopathy, arrhythmias, or connective tissue diseases including aortic dilation, aortic dissection, or mitral valve prolapsed[1]. In such syndromes or disease associations, aortic dilation or stenosis is sometimes one of the clinical findings as a main manifestation of the cardiovascular malformation[2,3]. Besides, facial dysmorphism and mental retardation are usually the extracardiac presentations seen in these patients. Some of the syndromes alike, for instance, DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, Opitz G/BBB syndrome (a genetic condition that affects several structures along the midline of the body) and Cayler cardiofacial syndrome (asymmetric crying face association), with different facial features and various degrees of mental retardation, have been proved to be of the same large deletion of the genes[1]. In Williams, Noonan and Down syndromes and VACTERL association, patients may also present with facial dysmorphism and mental retardation, but are associated with aortic stenosis rather than aortic dilation. However, there has been little discussion on what made these conditions have a predilection of facial and mental changes apart from the aortic dilation or stenosis, and how the genetic differences between these patients with aortic dilation and stenosis. In order to provide with a better understanding of such questions, it is necessary to make an overview of the clinical characteristics of such complexes on basis of the materials from the literature.

Materials and methods

Literature of the syndromes in association with facial dysmorphism, mental retardation and aortic dilation published between 1980 and 2012 was comprehensively retrieved in the MEDLINE database and the Google and Highwire Press search engines. The search was ended in December, 2012.

Results

Marfan syndrome

Marfan syndrome is an autosomal dominant connective tissue disorder, often involving the cardiovascular system, eyes, and skeleton. The diagnosis of Marfan syndrome is based on the clinical criteria and family history, termed as Ghent criteria. Revised Ghent nosologies that were proposed recently lay emphasis on aortic root aneurysm and ectopia lentis and recruited a little bit fewer patients comparing to the traditional criteria[4]. The major clinical features of Marfan syndrome include progressive aortic dilation and aortic valve incompetence, mitral valve prolapse and incompetence, lens dislocation and myopia, and a tall, thin statue with long limbs, arachnodactyly, pectus deformities, and sometimes scoliosis. Cistulli et al.[5] reported the details of the facial dysmorphism of Marfan patients, which were bimaxillary retrusion, a reduced maxillary length, an increased total anterior face height, a long lower anterior face height, an obtuse gonial angle, a steep mandibular plane, a reduced posterior nasal airway height, a reduced posterior airway space, and an increased distance from the mandibular plane to the hyoid bone. Marfan patients frequently have an above average intelligence quotient, however, they may have mental retardation and a deletion of chromosome 15q21.1q21.3[6].

The cause has been attributed to mutations in FBN1, the gene that encodes fibrillin-1. In the aortic tissue of healthy individuals, collagens that are usually derived from transforming growth factor-β (TGF-β) target genes, COL1A1 and COL3A1 are sufficiently expressed implicating an elevated TGF-β signaling pathway[7]. Marfan patients were pathologically evidenced of an excess amounts of collagens in the aortic media, and there showed an evidence of unique missense mutation in the of TGF-β receptor (TβR) II in Marfan's family members[7]. Ultrastructural observations found that the Marfan aortic media showed enlarged interlaminar spaces and loss of interlaminar elastic fibrils[8]. Enhanced nuclear phosphorylated Smad2 were found in the aortic tissues of classic Marfan's patients, which may be associated with mutations of TβRI or TβRII[9]. Hilhorst-Hofstee et al.[10] presented clinical features of 10 patients with a complete deletion of a FBN1 allele with seven patients fulfilling the Ghent criteria for Marfan syndrome. Aortic root dilation was present in 6 of the 10 patients. Two patients had motormental retardation and dysmorphic features.

Loeys-Dietz syndrome

Loeys-Dietz syndrome is a genetic disorder of the connective tissue involving cutaneous, cardiovascular, craniofacial, and skeletal systems. Fetal aortic root dilation has been described as a prenatal feature of the Loeys-Dietz syndrome[11]. LDS patients may have arterial tortuosity with widespread vascular aneurysm and dissection. Loeys-Dietz syndrome is similar to Marfan syndrome, including altered activity of TGF-β[12]. Unlike Marfan patients, patients with Loeys-Dietz syndrome do not have an FBN1 gene mutation; however, they have a TβRI or TβRII mutation[12]. Yetman et al.[13] did genetic studies for Loeys-Dietz syndrome by detecting DNA sequencing and found a missense mutation in the kinase domain of TβRII. Muramatsu et al.[14] described a heterozygous missense mutation of TβRII a patient with Loeys-Dietz syndrome type 1B who manifested facial changes (long palpebral fissures and a retrognathia), developmental delay, and progressive cardiovascular malformations (aneurysms of the aortic root and main pulmonary artery). Experiments on fibroblasts derived from Loeys-Dietz syndrome patients with TβRI mutations and those with TβRII mutations showed decreased expression of elastin and fibulin 1 genes with impaired deposition of elastic fibers in the former, but intracellular accumulation of collagen type I in the presence of otherwise normal elastic fiber production in the latter[15].

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome is a group of different inherited disorders characterized by weak connective tissues involving mainly the skin, joints, blood vessels and other organs[16]. The clinical manifestations of Ehlers-Danlos syndrome may vary with type. Marked joint hypermobility, skin hyperextensibility (laxity), and fragility are characteristics of the classic type of Ehlers-Danlos syndrome; joint

hypermobility is the major manifestation of the hypermobility type; and spontaneous rupture of arteries and very visible veins from the skin are the main features of the vascular type[17]. Aortic root dilation, usually of a mild degree, occurs in one-quarter to one-third of individuals with Ehlers-Danlos syndrome, classic and hypermobility types[18]. The severity appears to be much less than occurs in Marfan syndrome, and there is no increased risk of aortic dissection in the absence of significant dilation. Mental retardation of different degrees has been described in association with Ehlers-Danlos syndrome[19]. Children with Ehlers-Danlos syndrome may present progeroid facies[19]. Facial features (acrogeria) are one of the main features of most patients with the vascular type of Ehlers-Danlos syndrome[20]. They included acrogeriais (emaciated face with prominent cheekbones and sunken cheeks), sunken or bulging eyes, telangiectasia of the eyelids, and pinched thin nose and lips[21]. Studies have shown that ADAMTS2, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, PLOD1, and TNXB gene mutations have been implicated in the etiology of Ehlers-Danlos syndrome[16].

22q11.2 deletion syndrome

22q11.2 deletion syndrome, also known as DiGeorge syndrome, DiGeorge anomaly, velo-cardio-facial syndrome, Shprintzen syndrome, conotruncal anomaly face syndrome, Strong syndrome, congenital thymic aplasia, or thymic hypoplasia, is caused by the deletion of a small piece of chromosome 22[22]. Patients with 22q11.2 deletion syndrome may have heart defects, immune deficiency, kidney abnormalities, hearing loss, and cleft palate or other facial deformities[23]. It has been noted that 10 of 93 patients with 22q11.2 deletion syndrome with a novel cardiac finding of mild aortic root dilation without significant congenital heart disease to determine the number of patients with aortic root dilation[24]. The patients with 22q11.2 deletion syndrome have facial abnormalities, such as a long face, flat cheeks, hooded eyelid, a narrow mouth and cleft palate[25]. The diagnosis of this syndrome is based on the clinical presentation and genetic test, and the management strategies may vary according to the patients' presentation[25].

Larsen syndrome

Larsen syndrome includes a skeletal dysplasia, multiple joint dislocations, and characteristic facies. In addition, patients may have congenital heart defects and acquired mitral valve and aortic disorders. The aortic lesions can be similar to what can be seen in other connective tissue disorders in particular in Marfan syndrome. Marked aortic dilation and insufficiency and aneurysm of the ductus arteriosus were reported. Long tortuous aorta in addition to flattened facies, multiple joint dislocations and eye abnormalities was described in a three-year-old boy with Larsen syndrome[26]. Dilation of the aortic valve annulus, aortic arch, aortic root and ascending aorta was illustrated by computed tomography and echocardiography[26]. Multiple joint contractures and dislocations and abnormal facial appearance including hypertelorism were the initial clinical findings in the patients with Larsen syndrome[27]. The presence of cardiac abnormalities and cervical spine abnormalities were also noted[26]. Dominantly inherited Larsen syndrome was found to be heterozygous for missense mutations in FLNB[28]. Larsen syndrome locus, LAR1, was localized on chromosome 3p21.1-14.1[29]. The clinical overlap between Larsen and Loeys-Dietz syndromes makes differential diagnosis difficult and confirmatory genetic testing becomes important[30].

Temtamy -Shalash syndrome

Temtamy-Shalash syndrome is characterized by an association of craniofacial dysmorphism, coloboma and corpus callosum agenesis. It has been described in a family, in three children who presented with the same features: macrodolichocephaly, elongated face, arched eyebrows, antimongoloid slant of the eyelids, low-set ears, hypertelorism, bilateral “key-hole” coloboma of the iris, retina and choroid myopia, a beaked nose, long philtrum, short upper lip, micrognathia, and dental anomalies. Skeletal anomalies included brachydactyly of the hands and feet with bulbous thumb in one case, genu varum and flat feet. Two children as reported in the literature had aortic dilation and regurgitation. The condition was considered to be an autonomous syndromic entity with a likely autosomal recessive mode of inheritance[31].

Lujan-Fryns syndrome

Lujan-Fryns syndrome includes cognitive disabilities, characteristic behavioral patterns, facial anomalies, hypernasal voice, slender habitus with normal height, and increased span as well as cardiac anomalies[32]. Craniofacial features are long forehead, long narrow face, maxillary hypoplasia,

small mandible, long nose with high and narrow nasal bridge, short and deep philtrum, thin upper lip and highly arched palate[33]. Aortic root dilation in Lujan-Fryns syndrome is rare. Two patients reported by Wittine et al.[32] were with ventricular septal defect and aortic dilation, implicating a mutation in structural connective tissue gene. Thus, examinations of X-linked connective tissue genes may reveal the genetic cause.

Zimmermann-Laband syndrome

Zimmermann-Laband syndrome is characterized by changing presentations: coarse facial appearance, hepatosplenomegaly, and hirsutism in infancy, and gingival fibromatosis, small joint hyperextensibility, and hypoplasia of the finger- and toenails in childhood[34]. Mild to severe mental retardation is often a major presentation of such patients[35]. The reported patient was evidenced of aortic root dilation with dilated right heart, but normal left ventricular dimensions and systolic function but evidence of diastolic dysfunction, by echocardiography[34]. It was suggested that the candidate gene in Zimmermann-Laband syndrome was localized on 3pl4.3-p21, as it was noted a reciprocal translocation of chromosomes 3p21.2 and 8q24.3 in a mother and daughter with Zimmermann-Laband syndrome and in a male patient with translocation 3pl4.3 and 17q24.3[36].

Fragile-X Syndrome

Patients with fragile X syndrome have mental retardation or significant developmental delay[37]. Physical characteristics are usually subtle and consist of a long, thin face with large ears. It is caused by a trinucleotide repeat expansion (CGG) in the fragile X mental retardation gene (FMR1) at Xq27.3[38]. Cardiac disease may include mitral valve prolapse, which can be seen in up to 50% of adult patients with Fragile X syndrome. There are also incidences of mild dilation of aortic root in adults[39].

Turner (45X) Syndrome

Turner syndrome is a chromosomal condition that caused by complete or incomplete X chromosome affecting 1:2500 females[40]. About 10% of girls with this syndrome have heart defects, such as ventricular septal defect, coarctation of the aorta, bicuspid aortic valve, hypoplastic left heart, mitral valve prolapse and idiopathic aortic root dilation[41]. Although mental retardation is not a feature of Turner syndrome, however, this was found in Turner syndrome patients with ring chromosome X formation in a high incidence. Often, Turner syndrome patients have a triangular face with downslanted eyes[1], a flattened cranial base angle, a marked reduction in posterior cranial base length, facial retrognathism and short and posteriorly rotated jaws[42]. Nevertheless, the facial dysmorphism of Turner syndrome can sometimes be subtle[43].

Discussion

Syndrome is a collection of features that appear to occur over and over in a group of patients due to a specific chromosomal abnormality. In many syndromes, the chromosomal abnormalities may be risk factors contributing to the development of heart disease[1]. The above-mentioned syndromes/association are unexceptionally rare diseases, affecting a small percentage of the population, e.g., less than 200,000 persons in the United States, or about 1 in 1,500 people according the Rare Disease Act of 2002. The syndromes can be diagnosed at birth or in infancy, and even in prenatal period, based on clinical presentation and genetic tests. Unfortunately, there is no cure for the syndromes, but multidisciplinary management may be helpful for relieving the patients' symptoms.

There are several other heritable TGF-β-opathy syndromes with unique clinical features as well. The phenomenon that aortic dilation in association with the facial changes and mental retardation suggested a possibility of having a Marfan-related connective tissue disorder in these patients who might have FBN1, FBN2, TβRI and TβRII gene mutations[44]. Loeys-Dietz syndrome shows overlapping signs with alternative connective tissue disorders, due to different gene defects and characterized by vascular fragility, such as Marfan syndrome, Ehlers-Danlos syndrome (vascular type), and arterial tortuosity syndrome, due to SLC2A10 gene mutations and characterized by facial features, aneurysm ruptures, vascular tortuosity, and pulmonary artery stenosis[45]. In Loeys-Dietz syndrome, however, typical and easily recognizable characteristics that distinguish Loeys-Dietz syndrome type 1 from Marfan syndrome are hypertelorism, cleft palate or bifid uvula, generalized arterial tortuosity, craniosynostosis, patent ductus arteriosus, and atrial septal defect, whereas Loeys-Dietz syndrome type 2 patients demonstrate skin abnormalities, joint laxity, and rupture of visceral organs[46].

Syndrome	Prevalence	Age	Sex	Facial dysmorphism	Mental retardation	Aortic dilation	Other signs	Gene conditions	Management
Marfan	10~30/100,000	All ages	No sex predilection	Maxillary/mandibular retrognathia, long face and high, arched palate	Mental retardation Learning disability (rare)	Annuloaortic ectasia	Arachnodactyly, ectopia lentis,, dural ectasia	Mutations in the FBN1 gene on chromosome 15, elevated TGF-β levels	Indented chest operation surgical intervention to mitral and aortic disorders β- blockers medication prescription glasses or contact lenses
Loeys-Dietz	Unknown	Mean age at death 26.1 years	Not described	Ocular hypertelorism, bifid uvula/cleft palate, craniosynostosis	Mental retardation	Aneurysms or dissections of the aorta, arterial tortuosity and aneurysms in the peripheral arteries	Pectus excavatum or pectus carinatum Translucent skin	Causal TβR1 or TβR2 mutation excessive TGF-β signaling	Surgical repair of the aortic aneurysm
Ehlers-Danlos	1/2,0000~50,000 (type I/II), 1/1,0000~15,000 (type III), 1 /100,000~ 250,000 (type IV)	The sex-related prevalences are almost equal	Recognizable beginning in early childhood and is usually diagnosed in young adults	Progeroid facies	Mild mental retardation	28% had aortic root dilation14/42 in type I/II 6/29 in type III	Skin hyperextensibility, joint hypermobility, tissue fragility with ecchymosis or easy bruising	Mutations in the ADAMTS2, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, PLOD1, and TNXB genes	Physiotherapy, and anti-inflammatory drugs cardiovascular problems are treated in a standard manner
22q11.2 deletion	1/6000~1/6500	The median age at diagnosis was 4.5 years	Male prevalence (63%)	A long face, flat cheeks, hooded eyelid, a narrow mouth and cleft palate	Developmental delays and learning disabilities at an increased risk of developing mental illnesses: schizophrenia, depression, anxiety, and bipolar disorder	Mild aortic root dilation	Recurrent infections, autoimmune disorders, mild short stature and, less frequently, abnormalities of the spinal bones	The loss of a particular gene on chromosome 22, TBX1	Physical and speech therapy educational support, social, vocational and medical services surgery for heart defects and facial abnormalities
Larsen	1/100,000	Diagnose can be made in infancy	Gender predilection not mentioned	Flat face	Mental retardation in patients with Larsen syndrome was also observed	Marked aortic dilation	Multiple joint dislocation, and short fingernails, hearing loss	Larsen syndrome locus, LAR1, was localized on chromosome 3p21.1–14.1	Treatment of Larsen syndrome varies according to an individual's specific condition
Temtamy	<1/1,000,000			Elongated face	Mild mental retardation	Aortic dilation and regurgitation	Iris coloboma, agenesis of the corpus callosum	Homozygosity mapping excluded the genes ASXL2, ZNF462 and VAX1	
Lujan-Fryns	Rare, not yet determined	Most reports describe patients at adolescent and young adult age		Long forehead, long narrow face	X-linked mental retardation, cognitive disabilities	Aortic root dilation	Haracteristic behavioral patterns, hypernasal voice, slender habitus, and increased span	A novel missense mutation in the MED12 gene	Drugs, prescription medications, alternative treatments, surgery, and lifestyle changes
Zimmermann-Laband	No prevalence information has been added yet	All ages	Equal in gender	Coarse facial appearance	Mild to severe mental retardation	Marked aortic root dilation	Hepatosplenomegaly, and hirsutism in infancy and gingival fibromatosis, small joint hyperextensibility, and hypoplasia of the finger- and toenails in childhood	3pl4.3-p21	Surgical excision of the excess gingival
Fragile-X	1 in every 3600 males and 1 in 4000~6000 females			Elongated face, large or protruding ears	Intellectual disability	Aortic root dilation	Behavioral characteristics, flat feet, larger testes	Mutation of the FMR1 gene on the X-chromosome	Underlying cause treatment
Turner	1/2,500	Young infants and older females	Only female	Downslanting eyes, droopy eyelids, prominent earlobes, crowding of the teeth and a short webbed-like neck	A varying degree of mental retardation in 60% of the patients	Progressive aortic root dilation or dissection	Congenital heart defects, short height, infertility	Complete or incomplete X chromosome	Estrogen replacement therapy

Table 1: Syndromes with facial dysmorphism, mental retardation and aortic dilation.

Arterial tortuosity syndrome (ATS) is a heritable disease characterized by twisting and lengthening of the major arteries, hypermobility of the joints, and laxity of skin. In arterial tortuosity syndrome, loss of GLUT10 results in defective collagen and/or elastin, and the TGF-β activation may represent a secondary response to a defective extracellular matrix[47]. Arterial tortuosity and aneurysms of other arteries have been noted in patients with Loeys-Dietz syndrome in comparison to Marfan

syndrome. Mutations in TβRII are, therefore, associated with a spectrum of aortic disease syndromes, including Loeys-Dietz syndrome, Marfan syndrome and familial thoracic ascending aortic disorder. Aortic aneurysm osteoarthritis syndrome caused by Smad3 mutations presenting with aneurysms, dissections and tortuosity throughout the arterial tree in association with mild craniofacial features and skeletal and cutaneous anomalies may lead to increased aortic expression of several key cytokines in the TGF-β pathway. In contrast to other aneurysm syndromes, most of these affected individuals presented with early-onset osteoarthritis, with a genetic locus to chromosome 15q22.2-24.2[48].

Reexamination of patients with a TβRI or TβRII mutation revealed extensive clinical overlap between patients with Marfan and Loeys-Dietz syndrome[49]. The phenotypes of other syndromes share marfanoid habitus including a high stature, a long face, a long arm and dilation of the aorta, unexceptionally with a tendency of inherited connective tissue disorder (Table 1).

Some other syndromes like Williams syndrome present distinct facial features and mental retardation, but with stenosis of the great vessels. The dysmorphic facial feature can be a broad forehead associated with and variable intellectual disability[50]. Williams syndrome is a contiguous gene deletion syndrome, with deletions or mutations of the elastin gene and in adjacent genes of the locus 7q11.23[51]. Noonan syndrome is an autosomal dominant disorder with missense mutations in the PTPN11 gene on chromosome 12, encoding the nonreceptor protein tyrosine phosphatase SHP-2[43]. It is characterized clinically by short stature, typical face dysmorphology and congenital heart defects. The contour of the face becomes more triangular, the eyes are less prominent, and the neck appears less short with increasing age. The most common congenital heart defect of the syndrome is pulmonary stenosis (39%), and aortic coarctation and subaortic obstruction can also be seen[43]. Down syndrome is a chromosomal condition with an extra copy of genetic material on part or complete 21st chromosome[52]. It is characterized by mental retardation, dysmorphic facial features, and other distinctive phenotypic traits with impairment of cognitive ability and physical growth[53]. The facial characteristics are often microgenia, oblique eye fissures with epicanthic skin folds on the inner corner of the eyes, muscle hypotonia, a flat nasal bridge, a single palmar fold, a protruding tongue or macroglossia, a short neck, white spots on the iris known as Brushfield spots[54]. VACTERL association has been revealed by experimental studies mutations in Sonic hedgehog pathway genes, such as the Shh and the Gli genes[55]. This condition may have mild mental retardation (intelligence quotient = 60~65, and right-sided mandibular hypoplasia was reported as a characteristic face[56]. Whereas, aortic dilation is absent when the patients present with featured facies and mental retardation. Instead, aortic stenosis, aortic arch abnormality or other

Syndrome/Association	Prevalence	Age	Sex	Facial dysmorphism	Mental retardation	Aortic disorders	Other signs	Gene conditions	Management
Williams	1/7,500~20,000	From birth through adulthood	Equally prevalent in males and females	The "elfin" facial appearance, along with a low nasal bridge	Mild to moderate mental retardation	Supravalvular aortic stenosis	Idiopathic hypercalcemia	Deletion of the region q11.23 of chromosome 7	Multidisciplinary management
Noonan	1/1,000~2,500	From birth	Males and females are equally affected	Hypertelorism, downslanting eyes, webbed neck	25% of individuals with Noonan syndrome have mental retardation	Aortic root dilation is rare bicuspid aortic valve, coarctation of the aorta and a hypoplastic aortic arch	Short stature, and chest deformity	PTPN11, SOS1, RAF1, and KRAS gene problems	No specific treatment. Only for relieving symptoms. Growth hormone has been used successfully to treat short stature
Down	9.0~11.8/ 10,000 live births	Children and adolescents	Male 40%, female 60%	Microgenia, oblique eye fissures	Cognitive impairment	Aortic stenosis	Congenital heart defects	Trisomy 21 chromosomal defects	Anti-seizure and thyroid hormone replacement
Vacterl association	16 cases per 100,000 live births	Congenital birth defects, could be observed on prenatal ultrasound	A significant predominance of males	Right sided mandibular hypoplasia	Mild mental retardation (intelligence quotient = 60~65)	Aortic coarctation	Vertebral anomalies, anal atresia, congenital heart disease, tracheoesophageal fistula, renal dysplasia and limb abnormalities	Trisomy 18 chromosomal defects	Treatment should be multidisciplinary and include management of any cardiac anomalies

Table 2: Syndromes with facial dysmorphism, mental retardation and aortic stenosis.

types of aortic disorders can be present (Table 2).

As stated by Liu et al.[57], 9.8% patients had elfin faces and 7.8% had mental retardation in their 51 pediatric patients with congenital aortic stenosis, implicating a high frequency of facial dysmorphism and mental retardation associated with stenosis of the aorta or of the aortic valve.

A nonsense mutation of the ATRX gene causes mild mental retardation[58]. UPF3B protein truncation mutations can cause also nonspecific X-linked mental retardation (XLMR) and autism[59]. EP300 mutations may be associated with both mental retardation (a marked learning disability/cognitive impairment) and facial dysmorphism, which has been described in Rubinstein-Taybi syndrome[60].

Conclusions

The association of facial dysmorphism, and mental retardation, in particular in children, may lead to the diagnostic consideration of an aortic disorder. The dilated aorta in this association may mean a weak aortic wall caused by connective tissue fragility with mutational etiologies of the specific genes, including TGF-β signaling or X chromosome genes. Meanwhile, the aortic stenosis when associated with facial dysmorphism and mental retardation implicate alternative genetic malformations, such as mutation or microdeletion of ATRX, UPF3B, or EP300.

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