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Case report

Down syndrome with co-occurring Marfan syndrome

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SUMMARY

Down syndrome (DS) and Marfan syndrome (MFS) are two unique genetic disorders that share limited phenotypic overlap. There are very few reported cases in the existing literature on overlapping DS and MFS. Although these two disorders are phenotypically unique, features present in these cases are variable, resulting in mixed and dominant expressions of particular features. We present the first adolescent case of trisomy 21 associated DS and fibrillin-1 gene associated MFS in the literature who had a height at 90th percentile for an 11-year old boy and discuss the implications of this case in terms of future medical care when these two genetic syndromes are present in the same individual. Understanding of certain features of the 'non-dominating' syndrome is crucial for clinicians to recognise when DS co-occurs with MFS. Close monitoring of the cardiovascular, ophthalmologic and musculoskeletal systems is recommended if both syndromes are diagnosed given that both can be independently associated with disorders in these organ systems.

BACKGROUND

Down syndrome (DS) is the most common chromosomal disorder in the USA, with a prevalence of 1 in 824 live birth as of 2010.[1] DS is most often diagnosed by prenatal screening or by recognition of characteristic phenotypic features present in the newborn after birth.[2] The diagnosis of DS is confirmed by karyotype, wherein trisomy of chromosome 21 is observed. While nearly 95% of cases of DS are associated with trisomy of chromosome 21 related to a meiotic non-disjunction error, a minority of cases are associated with translocation between chromosomes 21:14 or somatic mosaic DS.[3]

Marfan syndrome (MFS) is a connective-tissue disease most frequently caused by mutations of the fibrillin-1 (FBN-1) gene, which is located on chromosome 15q21.1 and occurs with an autosomal dominant inheritance pattern.[4] MFS has a prevalence of approximately 1 in 5000 live newborns, with 75% patients have a family history of this disease and 25% having de novo mutations.[4]

Statistically, these two conditions (DS and MFS) would be expected to occur together, by chance, in approximately 1 in 5–10 million live births. MFS has some overlapping and some divergent phenotypic features with DS although given the infrequency of these conditions co-occurring, a specific phenotype associated with dual genetic mutation is unknown. Certain typical features of one syndrome may be diminished or amplified due to the presence of the other gene defect or triplication of gene product.

Here, we present the first case of an adolescent with both DS and MFS. The authors will elaborate on three issues: (1) What are the unique characteristics that should prompt clinicians to test for additional genetic disorders in DS patients? (2) What features of patients with both DS and MFS are needed to be monitored? (3) What are the possible aetiologies to phenotypic presentation in this specific overlap syndrome based on the genetic signatures of these patients?

CASE PRESENTATION

A 11-year-old boy with DS presented to the clinic with daily headaches for 6–12 months. Acetaminophen and ibuprofen were used multiple times a day to reduce the headache frequency with limited efficacy. As the patient was blind and non-verbal, it was difficult for parents and physicians to evaluate clinical features, although the patient was held his head repeatedly and cried 'ow'. There were no associated autonomic symptoms, nor focal neurologic signs during these attacks or any gait disturbances, although the patient preferred to lie down.

The patient was born at 34 weeks due to premature rupture of membranes to a 28-year-old, gravida 2, para 1, mother. Birth weight was 2438 g. He was intubated after delivery for 2 weeks and stayed in the neonatal intensive care unit (NICU) for 4 weeks. The patient walked at 18 months of age and spoke his first word at 14 months of age, although failed to gain significant developmental milestones thereafter. He is blind secondary to multiple retinal detachments, unable to communicate beyond one to two words and he is dependent on parents for nearly all activities of daily living.

The patient was diagnosed with DS shortly after birth following identification of a classic phenotypic facies. Karyotype later confirmed trisomy of chromosome 21. The patient had multiple comorbid diagnoses after birth including aphakia of eyes, retinal detachment, cataract, myopia with astigmatism, myopic retinopathy, ectopia lentis, congenital small ear canal, eustachian tube dysfunction, asthma, atrial septal defect (ASD), dilated aortic root, pulmonary regurgitation, mitral valve/tricuspid valve prolapse and insomnia. The patient had several prior surgeries including bilateral myringotomy, multiple retinal and cataract surgeries. Current active medications included: albuterol, losartan, dorzolamide ophthalmic eye drop and prednisolone ophthalmic eye drop.

There was no family history of either DS or MFS. The patient's father has a history of headache

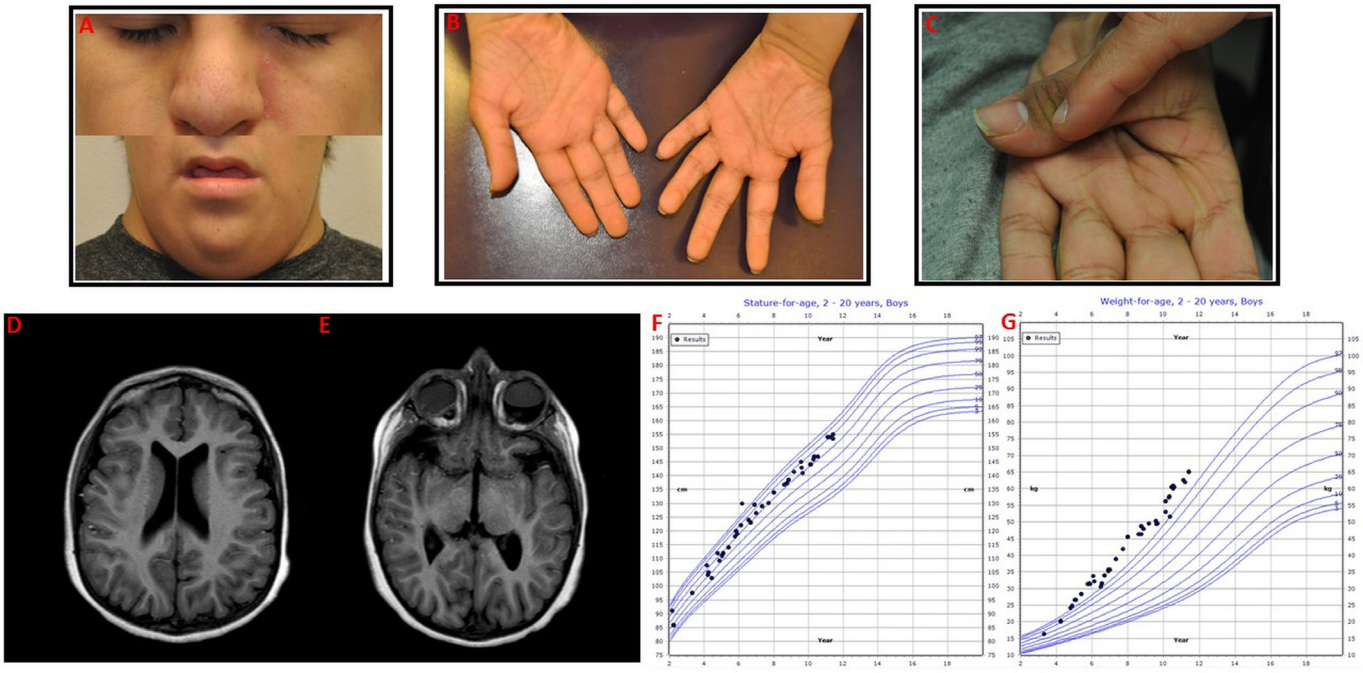

Figure 1 Phenotypic manifestations: (A) Small and upslanting palpebral fissures, smooth philtrum and micrognathia (consistent with DS); enophthalmos, elongated facies and no epicanthal folds (consistent with MFS). (B) Lack of brachydactyly, clinodactyly and single transverse palmar crease (observed in persons with DS). (C) Steinberg or thumb sign (when folded across palm, the distal phalanx of the thumb fully extends beyond the ulnar border of the hand). MRI images: (D) Axial T1 image demonstrating diffuse corticala trophy, diminished quantity of the white matter volume and mild-moderate thinning of the corpus callosum. (E) Axial T1 image demonstrating prominent extra-axial spaces at the anterior temporal lobes and ex vacuo ventriculomegaly. Orbital vault is small, consistent with multiple prior ophthalmologic comorbidities. Patient's growth charts: (F) Height growth chart (90th percentile at 11 years of age). (G) Weight growth chart (>97th percentile at 11 years of age). Not pictured: pectus excavatum is poorly visualised due to obesity. DS, Down syndrome; MFS, Marfan syndrome.

(tension type) and diabetes. In addition, no family history of epilepsy, intellectual disability, genetic disorders or other neurologic conditions.

The patient was noted to be normotensive (112/56 mm Hg) with a weight of 65.2 kg and height of 154 cm (BMI=27.5, 98.4th percentile). His physical examination was notable for brachycephaly with a head circumference of 54 cm (65th percentile). He had bilateral sunken orbits (left greater than right, figure 1A) with left hemifacial depression and midline hypoplasia. The patient also had upslanting palpebral fissures, malar hypoplasia and smooth philtrum. The patient had pectus excavatum of the chest (although his obesity makes this difficult to clearly visualise without palpation), but no cardiac or pulmonary abnormalities were auscultated on examination. His extremities and fingers were disproportionately longer and thinner than his midline body habitus (figure 1B,C). His arm span (135.9 cm) resulted in an arm span: height ration of 0.88.

INVESTIGATIONS

1. A comparison of the phenotypic features of both DS and MFS as well as comparative cases in the literature are presented in table 1.
2. Typical phenotypic manifestations and patient's growth charts are presented in figure 1.
3. DNA analysis.

This patient had trisomy 21 (non-disjunction cell division) and a pathogenic deletion identified in FBN-1 gene. The variant was an in-frame deletion of the genomic region encompassing exon 54 of the FBN-1 gene. It preserved the integrity of the reading frame.

4. Transthoracic echocardiogram

The patient had a secundum ASD, mild right atrial enlargement, normal left atrium, left and right ventricles, mild prolapse of anterior leaflet of the mitral valve with trivial insufficiency, mild tricuspid valve prolapse with mild insufficiency, mild aortic root dilatation and mild aortic insufficiency and mild pulmonary regurgitation.

5. MRI of the brain

Neuroimaging demonstrated decreased white matter volume with thinning of the corpus callosum. The cerebellar vermis was mildly diminutive in size and the lateral ventricles were mildly prominent, posteriorly, thought to be ex vacuo in nature. There was contour irregularity with abnormal signal within the right eye globe as well as fluid levels with the left eye globe consistent with the history of retinal detachment (figure 1D and E).

TREATMENT

During the first encounter, a wash-out period of frequent administration of acetaminophen and ibuprofen for 4 days was suggested. Patient was suggested to maintain hydration and he was started on naproxen 250 mg two times per day for 14 days with as needed use thereafter.

OUTCOME AND FOLLOW-UP

Headaches improved dramatically with this intervention, and on follow-up, the patient was doing well without clear additional events. The patient will continue to receive occupational therapy, physical therapy, speech therapy and vision therapy.

Table 1 Patient's phenotypic manifestations (adapted from Vis *et al*[9].

	DS	MFS	Vis *et al* [9]	Presented case	Eayrs *et al* [10]	Zarate *et al* [8]	Kurolap *et al* [7]
Dysmorphic features							
Head and neck							
Upslanting palpebral fissure	+	–	+	+			
Epicanthic folds	+	–	+	+			
Flat face/flat nasal bridge	+	–	+	+		+	
Malar hypoplasia	–	+	–	+		+	
Low-set small ears	+	–	+	+	+		
Fissured tongue	+	–	–	+			
High-arched palate	–	+	+	–			+
Microcephaly	+	–		–			
Brachycephaly	+	–	+	+			
Short neck	+	–		+			
Excessive skin at the nape of the neck	+	–	+	+		+	
Single transverse palmar crease	+	–	–	–			+
Space between the first and second toe	+	–	–	+			+
Neurologic							
Intellectual disability	+	–	+	+			
Hypotonia	+	–	+	+	+		+
Gastrointestinal							
Duodenal atresia	+	–		–			
Hirschsprung disease	+	–		–			
Coeliac disease	+	–		–			
Endocrine							
Short stature	+	–	+	–			
Tall stature	–	+	–	+			
Obesity	+	–	+	+			
Hypothyroidism	+	–	+	–			
Ocular							
Brushfield spots	+	–	–	–			
Strabismus	+	–	+	+			
Cataract	+	+	+	+			
Glaucoma	–	+		–			
Ectopia lentis	–	+	–	+			
Flat cornea	–	+	+	–			
Auditory							
Hearing loss	+	–		+			
Cardiovascular							
ASD/VSD/TOF/PDA/PFO	+/+/+/+/–	–	–	+/–/–/–/–	–/–/–/–/+	–/+/–/+/-	+/–/–/–/–
Dilatation or dissection of aorta	–	+	–	+	+	+	+
Dilatation of main pulmonary artery	–	+	–	+			
MVP	–	+	–	+			
Tricuspid regurgitation	+	+		+	+	+	
Pulmonary artery hypertension	+	+	–	–	+	+	+
Cardiomyopathy with biventricular enlargement	–	+	–	–	+		
Haematologic							
Leukaemia	+	–	–	–			
Skeletal							
Atlantoaxial instability	+	–	–	–			
Scoliosis	+	+	–	+	+		
Joint hypermobility	+	+	+	+			
Pectus carinatum/excavatum	–	+	–	+			+
Arachnodactyly	–	+	–	+	+	+	+
Ulnar deviation of wrists	–	+		+	+		
Pulmonary							
Obstructive sleep apnea	+	–	–	+			
Apical blebs	–	+	–	–			

Continued

Table 1 Continued

	DS	MFS	Vis *et al* [9]	Presented case	Eayrs *et al* [10]	Zarate *et al* [8]	Kurolap *et al* [7]
Congenital diaphragmatic hernia	+	+		–	Left hemidiaphragm and a right anterior diaphragmatic hernia		
Dermatological							
Seborrheic dermatitis	+	–	–	+			
Alopecia areata	+	–	–	+			
Striae atrophicae	–	+	+	+			
Other problems							
Immunodeficiency	+	–		–			

ASD, atrial septal defect; DS, Down syndrome; MFS, Marfan syndrome; MVP, mitral valve prolapse; PDA, patent ductus arteriosus; PFO, patent foramen ovale; TOF, tetralogy of fallot; VSD, ventricular septal defect.

DISCUSSION

In the literature, co-occurrence of two genetic syndromes has been reported. DS has been reported to have co-existence with Ehlers-Danlos syndrome,[5 6] Gaucher disease and spinal muscular atrophy,[7] Prader-Willi syndrome, craniofacial microsomia and Stickler syndrome,[8] as well as MFS.[7–10] Similarly, MFS associated with FBN-1 has been reported with malignant mesothelioma,[11] fibromuscular dysplasia and cystic medial necrosis,[12] rheumatoid arthritis and systemic lupus erythematosus.[13]

We report a very rare case of the coexistence of DS and MFS. To our knowledge, there are only four other similar cases that have been previously reported and none in the adolescent age range. Our patient had similar phenotypic features to prior reported patients. Notably facial features (upslanting palpebral fissure, micrognathia flat facies, low-set small ears, protruding tongue), core body frame and obesity were more consistent with DS; while the ectopia lentis, enophthalmos, elongated facies, aortic root dilatation, mitral valve prolapse (MVP), pectus excavatum, striae atrophicae and upper/lower extremities were phenotypically more similar to MFS (figure 1B,C). It is well established that individuals with DS demonstrate unique facial features, short stature and brachydactyly, while MFS demonstrate tall stature and arachnodactyly. In our case, and other cases that have been previously reported, there appears to be one dominant phenotype in terms of patient's stature and length of hands/fingers. Thus, the opposing phenotypes from these two syndromes (short stature/brachydactyly vs tall stature/arachnodactyly) would present with variable expression and incomplete penetrance, depending on which syndrome is dominant. As noted in table 1, some manifestations in persons with DS and MFS may prompt the need for additional testing. First, even though obesity is common in DS, tall stature and elongated wingspan raised our concerns for MFS because our patient was at the 90th percentile for height (figure 1F,G). Similarly, the arachnodactyly and ulnar deviation of the wrists were not consistent with DS, as persons with this condition typically have brachydactyly and no ulnar deviation. Second, our patient had mild aortic root dilatation/mild aortic insufficiency, mild pulmonary regurgitation and mild MVP, which are more commonly seen in MFS, and differs from classic DS associated cardiac abnormalities. Lastly, when ectopia lentis is an atypical finding in persons with DS.

One clinical advantage of diagnosing multiple genetic conditions in the same patient is to enhance screening of comorbid conditions. DS and MFS have overlapping phenotypes features, such as abnormal teeth, cataract, myopia, scoliosis, joint hypermobility, pes planus, tricuspid regurgitation and congenital diaphragmatic hernia. Both our case and that reported by Vis *et al* presented with cataract, myopia, joint hypermobility and pes planus. Once both syndromes are diagnosed, it would be appropriate to schedule close monitoring of the cardiovascular, ophthalmologic and musculoskeletal systems given the implications of comorbid disease in each.[8] Specifically, monitoring for disorders of the aorta, heart failure and retinal disease is warranted given that both genetic disorders can affect these systems. In all but one reported case of co-occurring DS–MFS, dilation of the aorta was present. Pulmonary hypertension, while not present in our case, was highly prevalent in other reports as well with one prior case identifying heart failure (which was secondary to late diagnosis of cardiovascular disease). Interestingly, there are no reported cases of haematologic malignancies in persons with DS and MFS, although the low patient volume in this series limits this observation's power.

The aetiologies to unique phenotypic presentation in this specific overlap syndrome remain elusive. Although trisomy of chromosome 21 is the hallmark of DS, there are other genes that may predispose to the heterogeneity of comorbid disease.[2] For example, DS has a higher risk of having juvenile myelomonocytic leukaemia comparing to healthy population and this disease is associated with a mutation of the NRAS gene, which is located on chromosome 1.[14] Hence, in DS and MFS co-occurring cases, we think that the dominating specific phenotypic manifestation (such as stature) would be decided by the processes of genetic transcription and genetic translation of that particular gene. On the other hand, gene interplay has been shown between DS and MFS and FBN-1 was found to be upregulated in patients with trisomy of chromosome 21.[15] There is a possibility of certain genes associated with DS and MFS yielding opposing phenotypes, resulting in compensational or mixed effects.[14] In our patient and others with similar genetic issues, compensational features are observed in cataract, myopia, joint hypermobility and pes planus. On the contrary, dominant expression exists in upslanting versus downslanting palpebral fissure, brachycephaly versus dolichocephaly, short stature versus tall stature and brachydactyly versus arachnodactyly.

To summarise, DS is one of the most common chromosomal abnormalities and when the provider is presented with a DS patient with atypical features, additional genetic review needs to be considered to ensure early diagnosis and interventions of other genetic syndromes. While rare, early identification of co-occurring genetic defects in a patient can allow for improved monitoring and possibly preventative intervention. This is also applicable for other aneuploidies when co-occurring with a

secondary genetic condition. Further, larger scale research is needed to investigate these unique set of disorders.

Patient's perspective

We understand that what our child has is a very rare combination of two diseases. We think our son is precious to us and what he has did not prevent us from loving him. In fact, we think he is just special, and he is a gift to us. We could not figure out what was going on when he started to develop headaches because he could not communicate with us. We are glad that now the medications are able to help him, and we will follow-up with the physicians for his health.

Learning points

- When Down syndrome (DS) is comorbid with Marfan syndrome, it leads to masking of certain classic features of the 'non-dominating' syndrome.
- Clinicians should recognise the possibility of more than one genetic diagnosis if an atypical finding in persons with DS is identified.
- Close monitoring of the cardiovascular, ophthalmologic and musculoskeletal systems is recommended if both syndromes are diagnosed.

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