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Contribution of Family History in Co-occurring Down Syndrome and Ehlers-Danlos Syndrome

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Abstract

Nearly all children with Down syndrome (DS) are born with hypotonia which later improves with age. We present a case of a 32-month-old female with DS who has persistent hypotonia and ligamentous hyperlaxity. She was subsequently diagnosed with Ehlers-Danlos Syndrome-Hypermobility type (EDS-HMT) based on family history, which resulted in the significant global developmental delay compared to age-matched peers with DS. Further clinical investigation is recommended in individuals with DS who appear to have developmental profiles significantly below what would be expected due to typical Trisomy 21 so that additional diagnostic testing and appropriate interventional therapy may be provided. Specifically, timely diagnosis of inherited disorders such as EDS-HMT is important in identifying other family members with the condition.

Keywords

Down syndrome; Ehlers-Danlos syndrome; Family History

Introduction

Trisomy 21, leading to Down syndrome (DS), is the most common genetic cause of intellectual disability/mental retardation with an incidence of 1 in 691 live births [1]. Almost all children with DS are born with hypotonia which improves with age [2]. Ehlers-Danlos

Syndrome-Hypermobility type (EDS-HMT) is an autosomal dominant, congenital connective tissue disorder characterized by large and small joint hyperextensibility, soft velvety skin, and normal scarring [3]. We describe a case of a 32-month-old female with DS with significant global developmental delays compared to other children with DS of the same age, prompting further clinical investigation. Based on the detailed family history, she was subsequently diagnosed with co-occurring EDS-HMT. Our report highlights the importance of a detailed family history in children with DS who do not make progress in their development, as other inherited conditions may be revealed that have consequences for other family members.

Case report

Our proband was suspected of having DS prenatally, based on the presence of a cystic hygroma and an atrioventricular canal defect. Postnatal chromosomal karyotype testing confirmed the diagnosis of 47,XX+21. She was born by spontaneous vaginal delivery at 36 ½ weeks gestation to a 40-year old Scottish/Irish mother (G4, P2) and a 38-year old Irish father. She had a birth weight of 3546 grams (>90%), length of 50 cm (75–90%), and a head circumference of 32.5 cm (25–50%).

Past medical history is significant for asthma, chronic lung disease, nystagmus, astigmatism, failure to thrive, gastroesophageal reflux disease, G-tube dependence, obstructive sleep apnea, and chronic otitis media. Since birth, she has had multiple hospital admissions due to aspiration pneumonia and chronic lung disease. Salient clinical features include persistent hypotonia and ligamentous hyperlaxity, poor head control and inability to sit independently at age 32 months. She was also non-verbal and expressed her needs and wants with gestures. The Bayley Scales of Infant and Toddler Development III conducted at a chronological age of 31 months 28 days of age revealed the following developmental levels: gross motor at 7 months, fine motor at 5 months, expressive language at 2 months, receptive language at 5 months, and cognitive at 7 months [4]. Based on the proband's significant global developmental delays and hypotonia, further diagnostic testing was initiated.

The Congenital Hypotonia Panel (SMN1 deletion, Prader-Willi and Angelman DNA methylation, Myotonic Dystrophy CTG repeat expansion, and Uniparental Disomy of Chromosome 14) and thyroid function studies (TSH = 2.5 and FT4 = 1.47) were negative. Further maternal family history revealed hypermobility in her grandmother. Additionally, her mother, uncle, half-sister, and half-brother are reported to have joint laxity without history of abnormal scarring. On exam, the proband and her mother had 8 and 9 out of 9 Beighton Hypermobility Scores respectively, suggesting they both have EDS-HMT. (Figure 1)

3. Discussion

Categorization of the Ehlers-Danlos Syndromes (EDSs) began in the late 1960s, formalized with the Berlin nosology published in 1988, and revised to its current system consisting of 6 major subtypes in 1997. Of these subtypes, EDS-HMT is considered the most common and is primarily characterized by joint laxity. Diagnosis is primarily based on family history and clinical features, as the causative gene is unknown [3]. Most previously reported cases of the

co-occurrence of EDSs and DS were published before the existence of a classification system which adequately discriminated between the different subtypes of EDS or phenotypically related conditions [5–7].

The co-occurrence EDS-HMT and DS has not previously been reported. Additionally, this case represents the first report on the combined developmental impact of these syndromes, and signifies the importance of obtaining a detailed family history in a child with DS and persistent hypotonia who is not progressing developmentally. Since co-existing EDSs and DS are infrequent, without awareness, their overlapping clinical features may lead to under-recognized incidence. Motor milestones for children with DS include rolling between the ages of 5 to 6.4 months, sitting independently between 8.5 and 11.7 months, crawling between 12.2 and 17.3 months, and walking independently between 15 and 74 months [8–9]. Our proband's inability to sit independently at the age of 32 months therefore represents a much greater developmental delay than would be expected of DS alone. In this case, a more detailed family history was able to elucidate a pattern of symptoms consistent with EDS-HMT among family members, pointing to a potential confounding inherited genetic condition.

While EDS-HMT is the most common subtype of EDS, the lack of a recognized gene mutation can make it difficult to diagnose. Joint hypermobility is the most clinically relevant feature, but this subtype of EDS can also be associated with musculoskeletal pain and joint dislocations. Some of the less commonly reported symptoms associated with EDS-HMT are also common clinical findings of DS. These include various gastrointestinal complaints, such as gastroesophageal reflux and constipation. Current treatment strategies for EDS-HMT focus on symptom management, although there are no specific guidelines to date.

In conclusion, this case is the first reported case to have a co-occurrence of DS and EDS-HMT. A detailed family history was important in making the final, correct diagnosis. Thus, individuals with DS who appear to have developmental profiles outside the range for DS should receive additional clinical investigation, including a family pedigree. A detailed family history of inherited conditions such as EDS-HMT is important because identification of a proband's affected family members will facilitate timely diagnosis of individuals who may be affected. These individuals will then have knowledge of the medical issues related to their condition, and may receive appropriate treatment if necessary. Diagnosis also decreases the diagnostic odyssey of symptomatic relatives who are being evaluated, often without attention to the family history.

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