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A rare case of 3C disease: Ritscher–Schinzel syndrome presenting with recurrent talipes equinovarus

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ABSTRACT

INTRODUCTION: Club foot (CF) is characterized by multiple deformities such as varus, adductus and internal rotation of the forefoot. It is well-known and a frequent congenital disorder. CF can concurrently be seen with several diseases but it can rarely manifest as a component of any other syndrome. Ritscher–Schinzel syndrome, or cranio-cerebello-cardiac syndrome, is rarely seen and has autosomal recessive inheritance. It is characterized by cranio-facial, cerebellar and cardiac abnormalities. We report a case diagnosed as Ritscher–Schinzel syndrome concurrent with persistent CF.
PRESENTATION OF CASE: A two-year-old boy with persistent CF and concurrent congenital hip dysplasia. Despite successful serial casting and subsequent achilloplasty a clinical relapse was observed in our patient. After a detailed phenotypic evaluation, genetical tests and imaging technique the patient was diagnosed 3C Ritscher–Schinzel syndrome.
DISCUSSION: A comprehensive literature review did not show any reports about concurrent hip dysplasia and clubfoot in Ritscher–Schinzel syndrome. We report that CF may be associated with rare genetical abnormalities.
CONCLUSION: With this report we would like to raise awareness about the possible association of persistent CF with this rare genetical disorder, Ritscher–Schinzel syndrome. It should be included in differential diagnosis of patients with persistent CF.

1. Introduction

Club foot (CF) is one of the most common deformities of the foot. The incidence, that varies depending on gender and race, is approximately 1%.[1,2] It is 2.5 times more common in male population.[2] Roughly half of the cases are bilateral and unilateral involvement is more frequent in the right foot.[1,3] There are three major components of CF: equinus, varus and plantar flexion.[4] Gastrosoleus muscle, attended by the long toe flexors tibialis anterior and tibialis posterior, is thought to have dominance in this condition. These muscles are found much smaller and shorter than any normal foot. Ponseti cast technique is often used for the treatment of CF.[2]

The purpose of treatment in CF is to obtain a normal anatomy as closest, to gain mobility and to have a painless foot. The etiology of CF has been investigated by numerous studies. Genetical factors, intrauterine mechanical factors, neuromuscular defects, intrauterine growth retardation, primary germ cell defects, myodisplasia, muscular imbalance, local dysplasia, eating disorders, hormonal disorders and infections have all been implicated in the etiology of CF.[5,6]

Ritscher–Schinzel syndrome, or cranio-cerebello-cardiac syndrome, is rarely diagnosed. It has autosomal recessive inheritance and it is characterized by cranio-facial, cerebellar and cardiac anomalies.[7,8] The typical cardiac manifestations are septal and AV canal defects. The characteristic central nervous system anomalies are Dandy–Walker malformation and cerebellar vermis hypoplasia, the latter leading to dilatation of the fourth ventricle and enlargement of the cisterna magna. Agenesis of the corpus callosum has also been reported.[9] The cranial dysmorphisms associated with 3C syndrome are heterogeneous and may include many deformities such as a large anterior fontanel, micrognathia, ocular hypertelorism, brachycephaly, low-set ears, slanted palpebral fissures, cleft palate, depressed nasal bridge and cleft palate with associated bifid uvula. Low-set ears are the most common cranial dysmorphism seen in 3C syndrome.[7] Life expectancy of the disease is in line with the severity of disease. The severity of cardiac and

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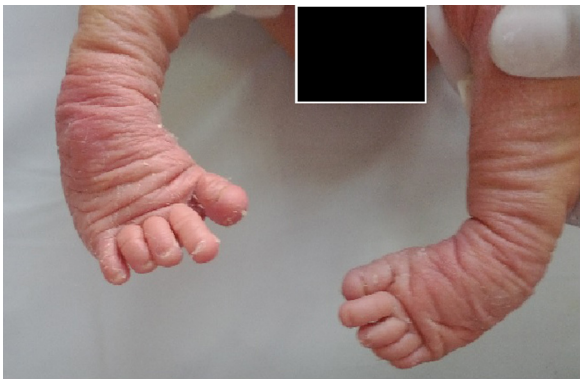

Fig. 1. Talipes equinovarus deformity (club foot) after casting.

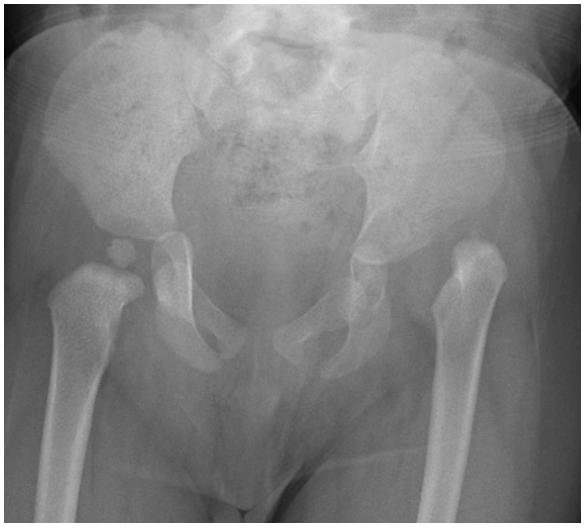

Fig. 2. Unilateral developmental hip dysplasia.

brain abnormalities determines survival. According to the literature, some patients died a few days after their birth whereas some being alive over the age of 40.

2. Presentation of case

Our patient was a 20-month old boy and the first child from his father's second marriage. He had no siblings. 35 year old mother did not have regular doctor visits during prenatal period. No consanguinity existed between his parents. Family had no history of any genetic diseases. He was born as a mature baby with a weight of 2800 g in the hospital. There was no history of hypoxia during pregnancy or birth. He never stayed in an incubator. He was still breastfeeding. His height and weight were under standard deviation. He had no epileptic seizures and no surgery to cause a sequelae of clubfoot. He had bilateral talipes equinovarus deformities (club foot) and had serial casting for five times at different clinics with Ponseti technique (see Fig. 1). Once recurrence was observed subsequent achilloplasty was performed. Pelvic radiography demonstrated developmental dysplasia of the hip on the left side (see Fig. 2). Patient had atypical facial shape and severe joint laxity. A comprehensive MRI assessment of the brain demonstrated Dandy–Walker malformation and also concurrent cerebellar vermis hypoplasia (see Fig. 3), a wide open anterior fontanelle, motor and mental retardation, micrognathia, microcephaly and retrognathia (see Fig. 4). After genetical evaluation and tests were performed the patient was diagnosed 3C (Ritscher–Schinzel) syndrome.

3. Discussion

Dandy–Walker syndrome (DWS) is a congenital brain malformation involving the cerebellum and the fluid filled spaces around. A key component of this syndrome is partial or even complete absence of some proportion of the brain which is located between the two cerebellar hemispheres (cerebellar vermis).[7] Our patient had various abnormalities in his brain MRI similar to those seen in DWS and also additional cerebellar vermis hypoplasia (Fig. 3). These findings together with typical facial abnormalities leaded us to consider Ritscher–Schinzel syndrome.[10–12]

DWS is a common manifestation of; Joubert syndrome, other 6p deletion syndromes and Ritscher–Schinzel syndrome and thus the differential diagnosis included all these syndromes.

Joubert syndrome (JS) is an autosomal recessive disorder characterized by hypotonia, growth retardation, episodic hyperpnea and/or apnea, atypical eye movements and truncal ataxia.[8] Together with these clinical features of the syndrome the neuroimaging hallmarks (MRI) of JS include cerebellar vermis

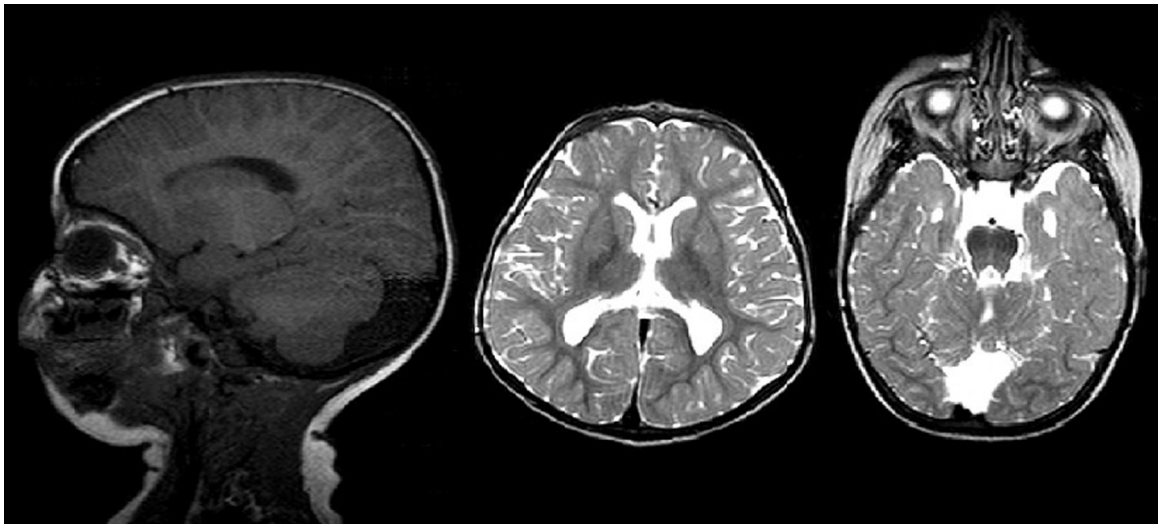

Fig. 3. Brain MRI image of our patient.

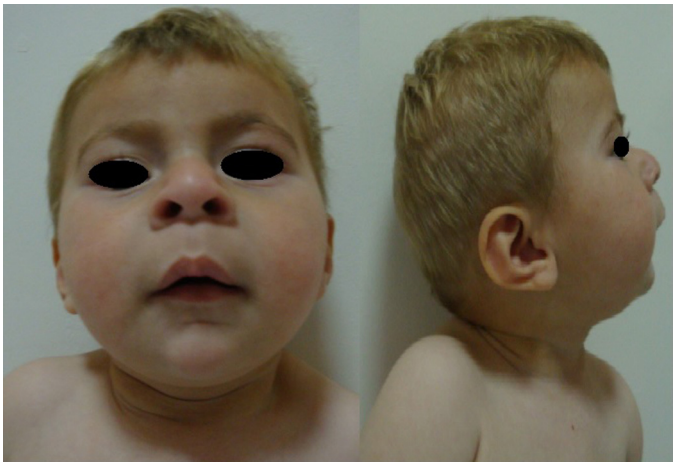

Fig. 4. Typical face appearance for 3C, Ritscher–Schinzel syndrome (anterior and lateral view).

hypoplasia and "molar tooth" sign (Fig. 5). Molar tooth sign results from a midbrain–hindbrain malformation characterized by thickened and elongated superior cerebellar peduncles, abnormally deep interpeduncular fossa and additional vermis hypoplasia.[13] So, lack of "molar tooth" appearance in our patient's MRI imaging helped us to exclude Joubert syndrome from differential diagnosis.

Patients with 3C syndrome often has 6p deletion however typical 3C syndrome phenotype was so prominent that we excluded other 6p deletion syndromes (Fig. 4).[8]

Ritscher–Schinzel syndrome include major cardiac anomalies such as ventricular septal defect, atrial septal defect, tetralogy of Fallot, double-outlet right ventricle, hypoplastic left heart, aortic stenosis, pulmonary stenosis and other valve anomalies (see Table 1). However, in some cases, cardiac abnormalities not reported. Our case also did not have severe cardiac abnormalities, but he had tricuspid valve insufficiency and left abberran band.[9,14]

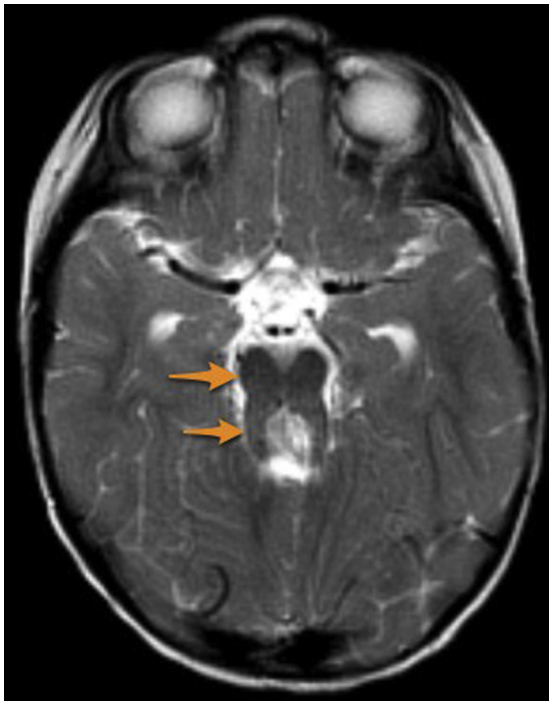

Fig. 5. "Molar tooth" sign. Arrows show thickened and elongated superior cerebellar peduncles, and abnormally deep interpeduncular fossa.

Table 1
Craniofacial, cardiac, cereballar and other malformations associated with 3C, Ritscher-Schinzel syndrome. (The malformations marked with "+" were manifest in our patient).

		Our case
Craniofacial malformation		
Low-set ears	58%	+
Hypertelorism	50%	+
Down-slanting palpebral fissures	40%	+
Depressed nasal bridge	36%	+
Prominent occiput	30%	+
Cleft palate	25%	+
Micrognathia	22%	–
Ocular coloboma	21%	
Cleft lip and palate	4%	
Cardiac malformation		
Septal defects	82%	+
Valvular defects	32%	–
Cono-truncal anomalies	14%	
Cerebellar malformation		
Dandy–Walker	68%	+
Dandy–Walker variant	21%	+
Hydrocephalus	11%	+
Other malformations noted in less than 10% of the patients		
Absent ribs	<10%	–
Adrenal hypoplasia	<10%	–
Anal atresia	<10%	–
Congenital glaucoma	<10%	–
Cutis aplasia	<10%	–
Hemangioma	<10%	–
Hemivertebrae	<10%	–
Hypospadias	<10%	–
Inguinal hernia	<10%	–
Malrotation of the gut	<10%	–
Nail hypoplasia	<10%	–
Nippler hypoplasia	<10%	–
Penis hypoplasia	<10%	–
Polydactyly	<10%	+
Renal malformations	<10%	–

Ritscher–Schinzel syndrome is caused by a mutation on the long arm of chromosome 8 at 8q24.13, the locus for KIAA0196, the gene for the protein strumpellin.[15] Strumpellin is highly expressed in skeletal muscle cells and mutations in it are also associated with spastic paraplegia. Strumpellin is involved in endosomal transport and cell death processes. The mutation occurs at a splice site and causes a substantial decrease in the amount of strumpellin produced by the cell.[16] We assume this deterioration in strumpellin might be responsible with a spectrum of musculoskeletal disorders such as CF or congenital hip dysplasia which were manifest in our patient. Our patient had also prominent joint laxity.

Surgery was planned for the treatment of congenital hip dysplasia at the time of patient's initial admission to our department. However after Ritscher–Schinzel syndrome was diagnosed, we considered his hip luxation as "teratologic" and according to the literature surgical treatment of teratologic hip luxation is often associated with unsatisfactory outcomes. After a comprehensive talk with the patient's family about his disease and probable unsatisfactory outcome with surgical intervention they decided for their child not to undergo any operation for hip luxation at this time.

4. Conclusion

Talipes equinovarus or club foot is a common disease and can be treated successfully with Ponseti method. However if a patient presents with recurrent CF, hip dislocation and atypical facial phenotype it is essential to consider a genetic disease in differential diagnosis. As mentioned above, a comprehensive review of literature demonstrated no reports about the association of persistent CF and Ritscher–Schinzel syndrome. So we report this case to raise

some awareness that persistent CF, in some cases, could be a feature of this rare genetical disorder, Ritscher–Schinzel syndrome.

Conflict of interest

We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Ethical approval

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Mehmet Nuri Konya: study concept, design, data collection, data interpretation. Muhsin Elmas: study design, data collection, data interpretation. Sadık Emre Erginoğlu and Murat Yeşil: study concept, design, data collection, writing the paper.

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