THINK ABOUT THE FOUNDER EFFECT IN ENDOGAMOUS POPULATION - CONGENITAL CATARACTS, FACIAL DYSMORPHISM, AND NEUROPATHY (CCFDN) SYNDROME - TWO CASES

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Abstract

Introduction: Congenital Cataract, Facial Dysmorphism and demyelinating Neuropathy (CCFDN) syndrome is a rare, progressive and multisystem disorder with autosomal recessive inheritance, to date described in 170 individuals of Roma ancestry (founder pathological variant c.863+389C>T in CTDP1 gene with high allelic endogamous frequency (7%)). Herein we present a familial phenotype shown by two siblings, aiming to increase awareness for the specific clinical presentation for a Romanian Roma ethnic subgroup.
Materials and Methods: Medical histories were obtained as a part of the affected individual's clinical workup. Molecular analysis of CTDP1 was performed in 2nd Faculty of Medicine of "Charles" University in Prague. Results: A 11-year-old boy presented with the pathognomonic triad after experiencing an episode of acute rhabdomyolysis. His sister aged 13 exhibited a similar phenotype. They both express a complex phenotype and additionally congenital right inguinal hernia. CCFDN was suspected and confirmed through targeted molecular analysis diagnosis by of the pathological variant in CTDP1 gene.Discussions and conclusions: This work highlights the essential tools in clinical practice and genetic counseling regarding CCFDN. Is inguinal hernia an additional feature to CCFDN phenotype or only an incidental finding? Based on the high allele frequency caused by founder effect, the pathogenic variant of CTDP1 is an actionable genetic variant. An earlier diagnosis in the girl, would've allowed prevention in the following pregnancies. The couple is aware of their high risk of another offspring with CCFDN, as all Roma endogamous subpopulation should be informed about.

Key words: CTDP1 gene, founder effect, Roma ethnicity, actionable genetic variant

Introduction

A Congenital Cataract, Facial Dysmorphism and demyelinating Neuropathy (CCFDN) (OMIM 604168) syndrome is a rare, complex developmental, multisystem disorder with autosomal recessive inheritance, to date found only in population having Roma/Gypsy ancestry. Clinically, it presents with the pathognomonic triad of bilateral congenital cataract, developmental delay and later demyelinating neuropathy [1]. First described by W-Muller-Felber et al. as a subtype of Marinesco-Sjogren syndrome (OMIM 248800) in 1998 (Marinesco Sjogren Syndrome with Rhabdomyolysis [2]), it was in 1999 when Tournev I. at al. established the molecular difference between the two entities although the 2 disorders share some overlapping features (congenital cataracts, delayed psychomotor development, and ataxia [3]) and gave the disorder's name [1]. Also in 1999, Tournev's team member, Angelicheva et al., by linkage studies, assigned the CCFDN locus to chromosome 18q23-qter (telomeric region of chromosome 18q), linkage disequilibrium and highly conserved haplotypes suggesting genetic homogeneity and founder effect [4].

The complex but particular phenotypic features of CCFNN allow a relatively rapid and accessible clinical diagnosis, thus herein we aim to increase awareness for the specific clinical presentation for a Romanian Roma ethnic subgroup by emphasizing the importance of a proper anamnesis and clinical workup for the diagnosis and further management, and subsequent genetic counseling.

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Phenotype evolution	C.C., ♀, 13 year-old, 1st born		R.C., ♂, 11 year-old, 2nd born	
Antenatal information	No particular events, normal fetal movements		No particular events, normal fetal movements	
Birth related information	Full term, normal vaginal delivery, normal weight at birth (2800 g), no hypotonia- affirmative to mother	Right inguinal hernia	Full term, normal vaginal delivery, normal weight at birth (3150 g), no hypotonia- affirmative to mother	Right inguinal hernia
Neonatal period	No particular events, no feeding difficulties, normal weight gain		No particular events, no feeding difficulties, normal weight gain	
Growth	Weight at percentile 10-25% for age	Height at percentile 10-25% for age	Weight at percentile 10% for age	Height at percentile 10-25% for age
Dysmorphic facial features	Prominent midface with a well-developed nose, thickening of the perioral tissues, and micrognathia (Figure 1)		Prominent midface with a well-developed nose, thickening of the perioral tissues, and micrognathia (Figure 2)	
Ophtalmological involvement	Bilateral congenital cataracts diagnosed one week after birth, she undergone surgery in both eyes at the age of 6 years with subsequent left eye aphakia and right eye pseudoaphakia, with a re-intervention 2 years after: no improvement in her visual impairment, bilateral cecity		Bilateral congenital cataracts diagnosed in the first days of life, he undergone surgery in both eyes at the age of 4 years, with subsequent aphakia, no re-intervention, bilateral cecity	
	Bilateral convergent strabismus since birth		No strabismus in infancy, developed bilateral convergent strabismus after the first year of live	
	Bilateral persistent hyperplastic primary vitreous in the anterior chamber		-	
	Bilateral proliferative vitreoretinopathy		-	
	Bilateral horizontal pendular nystagmus		Bilateral mixed horizontal-torsional nystagmus	
	Microphthalmia		Microphthalmia	
	Microcornea (mean diameter ~9 mm)		Microcornea (mean diameter ~7 mm)	
	Micropupils with fibrotic margins		Micropupils with fibrotic margins	
			Left eye ptosis	
Parainfectious rhabdomyolysis	No episode to date		One episode (5 months ago, at the age of 10 years and 10 months)- acute severe proximal weakness and myalgia with impossibility of walking and lifting the arms greater than a 90° angle, occurred after a febrile infection, along with rhabdomyolysis, myoglobinuria, and hyperCKemia (93404 U/L at first determination, diminished in 2 weeks with proper hydration and prednisone therapy to 361 U/L).	
Peripheral nervous system involvement	Delayed motor skill acquisition from the first year of life: - she sat approximately when 1 year and 2 months old - she started walking by the age of 3 years old, with ataxia gait, affirmative to the mother		Delayed motor skill acquisition from the first year of life: - he sat approximately when 1-year-old - he started walking by the age of 1 and a half years old, with normal gait, but gaining ataxia around the age of 3 years, affirmative to the mother	
	She was initially diagnosed with spastic quadriparesis		-	
	Currently presents loss of distal tendon reflexes, no sensory impairment in hands and feet		Currently presents loss of tendon reflexes, sensory loss in feet	
	No nerve conduction velocity measurement was performed		Symmetric and distally accentuated hypomyelinating peripheral neuropathy with predominantly motor involvement shown by measuring the nerve conduction velocity (in the context of his recent episode of rhabdomyolysis, with no previous records) in left peroneal nerve (9.2 m/s (-81.7%)) and right peroneal nerve (3.4m/s (-93.2%)); diminished bilateral M-wave amplitude (0.1 mV (-98%)); prolonged distal motor latency and residual latency (21.6 ms (+978%)). Sensory nerve action potentials were unobtainable, with no sensitivity to pain showing secondary axonal loss	
	No electromyography performed		Electromyography performed for bilateral anterior tibial muscles has shown myogenic changes (in the context of his recent episode of rhabdomyolysis)	
Central nervous system and psychological involvement	Delayed intellectual development: she started to talk around age 3 years; in present, mild cognitive deficit QD=50-55 (Portage Assessment Scale) with partial autonomy, some oculogyric and gestural stereotypies and adaptation difficulties		Delayed intellectual development: he started to talk around age 2 years; mild to moderate cognitive deficit QD=50 (Portage Scale) with partial autonomy, some behavioral stereotypies, psychoaffective immaturity and adaptation difficulties	
	No brain imaging performed to date		No brain imaging performed to date	
	Epilepsy with generalized tonic-clonic seizures between the age of 1 and 3 years old, responsive to usual antiepileptic drugs (clonazepam, carbamezepine)		No seizures	
	Electroencephalogram: performed in early childhood, data unavailable		Electroencephalogram: theta rhythm, medium amplitude waves with no pathological graphic elements	
Skeletal deformities	Mild thoracic levoscoliosis		Mild lumbar dextroscoliosis	
	-		Pectus excavatum	
	Genu valgum with bilateral atrophy of the short toe extensor muscles, externally rotated feet, high arched feet (Figure 1)		Genu valgum with bilateral atrophy of the short toe extensor muscles, externally rotated feet, high arched feet (Figure 2)	
Sexual development	Appropriate for age		Appropriate for age	
Other	-		An additional cardiologic finding was described for the boy in the context of a single-episode lipothymia and this is an aortic bulb ectasia not reconfirmed in the last cardiological evaluation this year.	

Table 1. Medical data of the two siblings

Materials and Methods

Medical histories were obtained as a part of the affected individual's clinical evaluation. Neurophysiologic study of affected muscles and nerves in the proband was performed. Molecular analysis of CTDP1 was performed in Charles University in Prague and University Hospital Motol, Prague, Czech Republic, a research laboratory interested in CCFDN subgroup of patients.

Written informed consent from the guardians of the two children and authorization for disclosure of recognizable persons in photographs for publication were obtained; patients and parents were given the opportunity to review the manuscript

Results

We report a family with four children of which the oldest two (one boy age 11 years and one girl 13 years) are affected. They have two younger siblings with no sign of the disease. Parents were endogamous, but not consanguineous. Parents reported a maternal grand-grandmother having congenital cataract, possibly suggesting another affected person, however she was not available for clinical evaluation. Both paternal grandparents have congenital strabismus. Medical data of the two affected siblings is detailed in Table 1 and the phenotype can be observed in Figures 1 and 2.

Routine laboratory tests did not reveal any relevant modifications excepting for the ones expected in the context of the boy's episode of parainfectious rhabdomyolysis.

Genetic testing

Subsequent to this episode of parainfectious rhabdomyolysis and presenting these mild dysmorphic features, he was oriented to Genetics Department where the suspicion of CCFDN was for the first time brought in discussion. Targeted molecular analysis by classic sequencing confirmed homozygous status of the pathological variant c.863+389C>T in the intron 6 of CTDP1 gene in the boy.

His older sister was also diagnosed with CCFDN presenting a striking similar phenotype.

Genetic counseling was offered for the affected family and consisted in:

- As known, CCFDN is an autosomal recessive disease. Thus, both parents of an affected child are obligate heterozygotes (i.e., carriers of the pathogenic variant of CTDP1 gene on one of the two alleles), but asymptomatic. Siblings of an affected person have a 25% risk to also carry the two pathogenic variants inherited from their parents, or a 50% risk to be asymptomatic carrier as their parents, or a 25% chance to not be a carrier, nor affected by the disease. On the other hand, the offspring of an individual presenting CCFDN are obligate heterozygous for the pathogenic variant. This becomes very important when the reproductive partner has also a risk to be a carrier (risk elevated at 7% by being part of the same Roma endogamous community);
- Carrier testing and genetic counseling was offered to the extended family before planning a pregnancy with an individual of Roma ethnicity

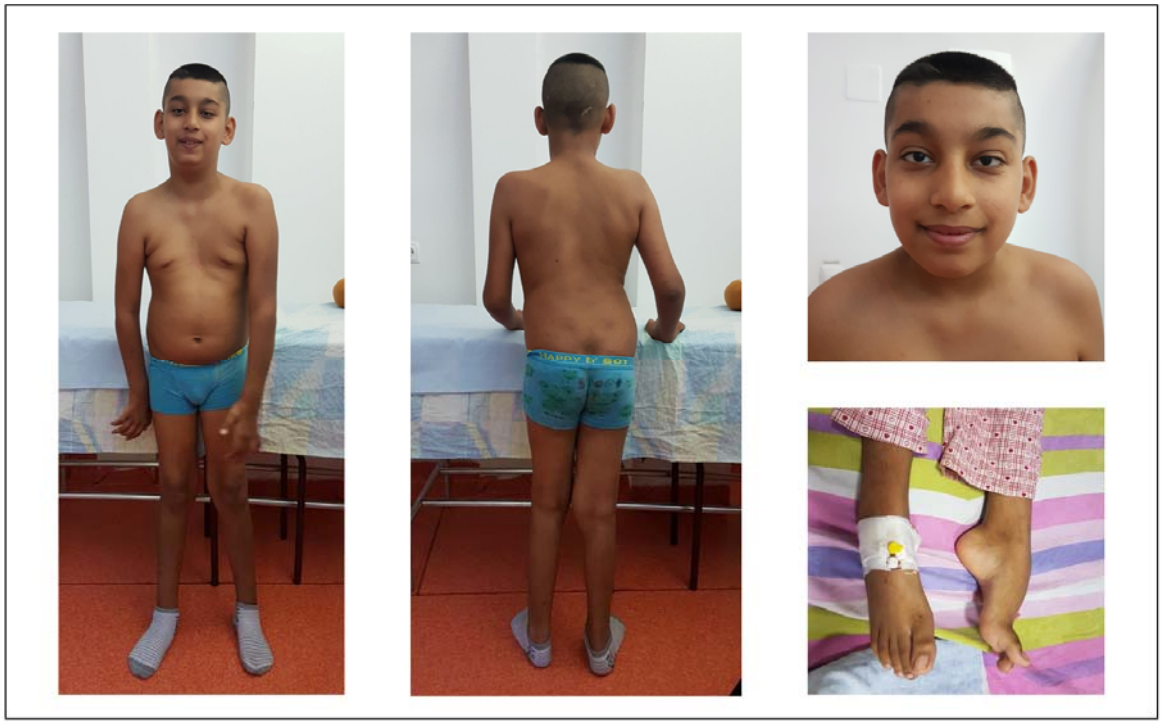

Fig. 2. Phenotypical features of patient C.R., ♂ 11 year-old

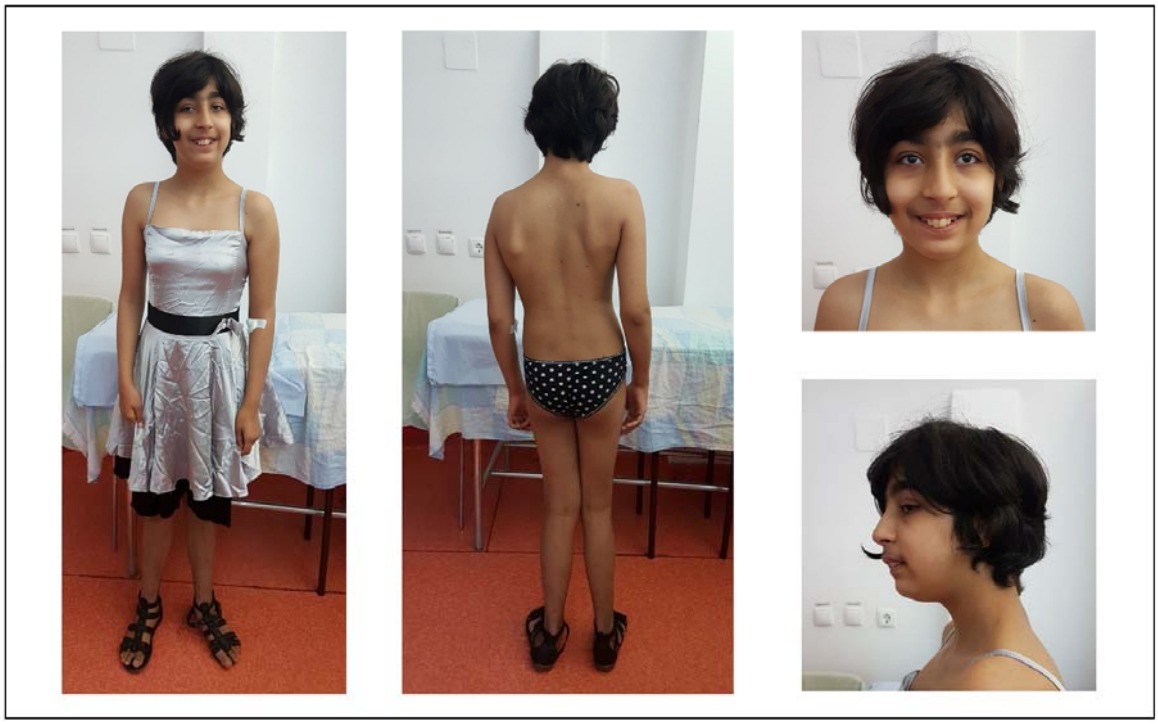

Fig. 1. Phenotypical features of patient C.C., ♀, 13 year-old.

Discussions

Apart from the pathognomonic triad described in the disorder's name, the phenotype described in literature includes additional features involving the anterior segment of the eye, the skull and face, the nervous system, and the endocrine system [5,6]:

- The eye involvement is present at birth and precedes the onset of neurological symptoms, with a severe visual impairment. The lens opacities are bilateral and often consist of anterior and posterior subcapsular opacities with clouding of the adjacent part of the lens nucleus or as total cataracts involving the entire lens. Axial length measurements may document microphthalmia and microcornea (mean diameter ~7.5 mm). Micropupils with fibrotic margins, sluggish responses to light and dilatation to mydriatics were also described as congenital. Later, some patients may develop bilateral ptosis, strabismus and horizontal pendular nystagmus. No fundus abnormalities are present [7,8]. Our two patients present the almost complete eye involvement with no ptosis yet in the girl.
- Facial dysmophism develops with age and are more evident in adult males. They include a prominent midface with an over-developed nose, thickening of the perioral tissues, forwardly directed anterior dentition, and micrognathia [9]. Both siblings here presented respect the mild facial dysmophism excepting the anomaly in dentition.
- The nervous system involvement is characterized by a symmetric and distally accentuated hypomyelinating peripheral neuropathy with predominantly motor involvement which becomes evident during childhood (invariable delay in early motor development with unsteady gait around 2-3 years of life) and progresses to severe disability by the third decade of life [3,9]. Nerve conduction velocity is normal in infancy but begins to decline around the age of 18 months, stabilizing at approximately 20 m/s at around age four to ten years. Electromyography shows myogenic changes in proximal muscles in rhabdomyolisis weakness episodes, recovered after [5,10]. The central nervous system is also affected with slow early intellectual development [10] and common cerebellar manifestations with ataxia, nystagmus, intention tremor, and dysmetria [11]. All these modifications were variable lined to brain MRI findings (from no abnormality to myelin immaturity and cerebral, cerebellar, and cervical spine hypotrophy, enlargement of the lateral ventricles, hyperintense lesions in periventricular white matter and brain stem) [11]. In our proband (C.R, ♂, 11 years old), the complex neurological

evaluation allowed us to assess the progression of CCFDN to date and assume the further evolution.

- Other involvements include reported intrauterine growth restrictions [12] (not presents in our patients) and small stature and low weight in some patients (intermittently described in the evolution of our two patients), skeletal deformities causing reduction of the respiratory capacity, secondary to the peripheral neuropathy (deformed feet and hands, thorax, spine) (both patients express all these acquired skeletal deformities), hormonal deficiency (growth hormone, hypogonadotropic hypogonadism), osteopenia [9]. The most feared part of the phenotype remains parainfectious rhabdomyolysis being a potentially life-threatening complication that leads to acute kidney failure characterized by acute severe proximal weakness and myalgia [5]. One episode of rhabdomyolysis in our boy's medical history was the essential point which suggested CCFDN diagnosis.

As already said, CCFDN diagnosis in mainly based on clinical findings. However, especially when the patient is the first in his family with this suspicion, the molecular confirmation must be done. CTDP1 is the only gene in which pathogenic variants are known to cause CCFDN. Targeted analysis identifies the pathogenic variant IVS6+389C>T in intron 6, the CTDP1 founder variant in the Roma ethnicity. CTDP1 maps to 18qter encoding a protein phosphatase whose only known substrate is the phosphorylated serine residues of the carboxy-terminal domain of the largest subunit of RNA polymerase II, indicating that CCFDN affects basic cellular processes of gene expression and developmental regulation [13].

The total number of affected individuals to date is approximately 170, all of Roma ethnicity [14]. The carrier rate for the c.863+389C>T pathogenic variant is approximately 7% among the Rudari (the Roma group most affected by the disorder) and approximately 1.4% in the general Roma population [15]. Allele frequency is extremely important for interpretation of variants and needs to be taken in account for founder effect in a given endogamous population. Cases of CCFDN were previously described by a group of paediatric neurologists in Romanian Roma ethnicity patients, but a carrier rate of the pathogenic variant in CTDP1 was not established yet [16,17].

The major differential diagnosis is the autosomal recessive Marinesco-Sjögren syndrome (MSS), similarly featuring cerebellar ataxia due to cerebellar atrophy, early-onset bilateral cataracts, chronic myopathy, variable intellectual disability and delayed motor development, along with short stature, dysarthria, strabismus, and nystagmus caused by mutations in the SIL1 gene [18]. Another similar disease is Galactokinase deficiency (OMIM 230200), an autosomal recessive rare mild form of galactosemia caused by another founder variant in Roma ethnicity (p.Pro28Thr in GK1 (GALK1)) characterized by early onset of cataract and an absence of the usual signs of classic galactosemia (feeding difficulties, poor weight gain and growth, lethargy, and jaundice. Because of the congenital cataract, Galactokinase deficiency is the main differential diagnosis of CCFDN in infants of Roma ethnic group [19,20]. As previously discussed, CCFDN was highly suspect in the proband and differential genetic diagnosis was postponed and later not needed.

Regarding the management and taking in consideration recent diagnosis of CCFDN in the two patients, recommended evaluations to establish disease's expression following initial diagnosis are to be completed with neurologic and orthopedic examinations, measurements of nerve conduction velocity for the girl, and brain MRI together with endocrinologic and bone density assessment for the two siblings.

Ethyologic treatment for CCFDN has not been discovered to date. Treatment of manifestations for the two children will respect the recommendations [14] and will focus on regular rehabilitation for peripheral neuropathy and to prevent osteopenia, corrective surgery for the secondary bone deformities, Vitamin D supplementation and hormone replacement therapy especially for the young girl if she is later diagnosed with amenorrhea. As the long-term outcome depends on the recurrence of rhabdomyolysis episodes it is very important to be aware and prevent rhabdomyolysis following viral infections and seek medical attention in emergency when suspected. If concluded, oral corticosteroid treatment for two to three weeks can result in full recovery within two to six months [5]. Other potentially life-threatening complications previously described are related to anesthesia (pulmonary edema, inspiratory stridor, malignant hyperthermia, and epileptic seizures) [21].

For follow-up, annual examinations including ophthalmologic, neurologic, and endocrine assessments were indicated.

Right inguinal hernia was our common case particularity, not previously described by any author in CCFDN. It remains the question whether there is an additional phenotype finding or just an incidental one.

Conclusions

This work highlights the essential tools in clinical practice and genetic counseling regarding Congenital Cataracts, Facial Dysmorphism, and Neuropathy. Based on the high allele frequency caused by founder effect, the pathogenic variant in CTDP1 causing CCFDN could've been and it still is an actionable genetic variant in this family. An earlier diagnosis in the girl, would've allowed a prenatal testing for the boy or at least a neurological and ophthalmological oriented fetal evaluation. The couple affirms they do not plan other pregnancies, but they are now aware of their high risk of another offspring with CCFDN, as all Roma endogamous subpopulation should be informed about. leukomalacia, intraparenchymal hemorrhage, cerebral atrophy, porencephaly, and hydrocephaly.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgements

The authors thank to Professor Pavel Seeman and his collaborator Petra Laššuthová working in the DNA

Laboratory from the Second Faculty of Medicine, Department of Paediatric Neurology, "Charles" University in Prague and University Hospital Motol, Prague, Czech Republic for their contribution in the molecular diagnosis of this cases and to the patients and their family for their participation in this scientifical paper.

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