CASE REPORTS

Congenital Cataracts – Facial Dysmorphism – Neuropathy syndrome

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ABSTRACT

A Gypsy girl with bilateral cataracts manifesting in the first year of life, psychomotor retardation, facial dysmorphism and motor delay, had experienced three episodes of parainfectious rhabdomyolysis until the age of 9. Sural nerve biopsy revealed a demyelinating peripheral neuropathy. All these features suggested the diagnosis of Marinescu-Sjogren syndrome or a related syndrome recently described in the Gypsy communities as Congenital Cataracts-Facial Dysmorphism-Neuropathy syndrome. Sequencing of the CTDP1 gene revealed homozygosity for the mutation IVS6+389 C>T in intron 6, confirming the diagnosis of CCFDN syndrome.

Key words: congenital cataracts, facial dysmorphysm, neuropathy syndrome

BACKGROUND

Congenital Cataracts-Facial Dysmorphism-Neuropathy syndrome (CCFDN) is an autosomal recessive complex developmental disorder, described in specific gypsy groups. This recently delineated entity shows major clinical overlap with **Marinesco-Sjogren syndrome (MSS)** (1).

The latter is an autosomal recessive disease as well, characterized by cataracts, ataxia, small stature, mental retardation, ***chronic myopathy, and, occasionally, peripheral neuropathy and acute rhabdomyolysis.*** The main symptoms of the CCFDN syndrome are already represented in the name of this disease. The diagnosis is confirmed by molecular genetic testing, based on homozygosity for a mutation in the ***CTDP1*** gene.

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Management consists in surgical treatment of the cataracts, rehabilitation, and corrective orthopedic surgery for the peripheral neuropathy allowing an acceptable quality of life and survival into adulthood. ❑

OBJECTIVE

To describe a little girl's case who presented with congenital cataracts, mild ataxia, hypotonia, acute rhabdomyolysis, somatic and mental retardation initially considered as a possible case of MSS. ❑

CASE PRESENTATION

A 9-year-old girl, S.G, of gypsy origin, from Bucharest, with numerous admissions in our hospital starting 2004, presented two remarkable aspects: bilateral congenital cataract and psychomotor retardation. The child, under her grandmother's guardianship, walked with many difficulties and started speaking late, around the age of 2 years. She was a "floppy infant" and the diagnosis of cerebral palsy was considered. No distinctive facial appearance was noted. She underwent three ocular interventions (replacement by an intraocular lens implant) at 3 years (12/2001), at 6 years (06/2004) and 9 years (06/2007) without any remarkable improvement (amblyopia). The child remained hypotonic, with evident difficulties to sit, despite the affirmative acquisition of sitting (she "never can stay alone on her toilet", grandmother said) and did not learn to run. Her gait was always uncertain, hesitant, staggered (frequent falls!), and wide-based (ataxia). Her grandmother's impression was "it seems like she hasn't force enough in her lower legs". Gower's maneuver was positive. She climbed stairs with difficulty and fatigue appeared after ~ 200 meters walking distance.

Between 18 and 27 December 2004 (six years old) the patient was hospitalized in our Pediatric Clinic with **a possible "Systemic Onset-Juvenile Idiopathic Arthritis":** high spiking fever for 18 days, arthralgias (right shoulder, left knee), painful cervical spine, myalgias. Other signs and symptoms were headache, abdominal pain, and dorsal paravertebral myalgias. Leukocytosis (42.000/mmc) with neutrophilia (85%), CRP positive (++++), ESR 62mm, and mild anemia (Hb 10.8g/dL) seemed to support this diagnosis.

Platelet counts were within normal limits. Bacterial infections (urine, blood, CSF cultures were negative), peritonitis (normal ultrasound exam) and malignancy were ruled out. CT (cranium) was normal. Steroid therapy for 5 months induced remission of all signs and symptoms described above. The patient did not develop arthritis within the next 4 years. Unfortunately, CK values have not been measured during the first and second episodes.

A second febrile episode with myalgias and vomiting (September 2006, ~7 days duration) and, *the last (the 3rd),* 11 days duration (23.01-02.01.2007) with high fever, myalgias (thighs), arthralgias (knees, hip), cervical and dorsal spine pain, lumbar pain, abdominal pain and vomiting, were investigated and treated in our hospital.

The history is relatively normal. She was delivered at term by a 17-year-old G1/P1 woman on December 8, 1998. Birth parameters were within normal ranges (weight 3400g, length 50cm, head circumference unknown). Apgar scores were not available. The neonatal period was also uneventful. She has been breastfed for the first 3 months and later fed with infant formula. Solid baby food was started at the age of 7 months.

The *neurological development* was delayed: she could hold the head up not until the age of 6 months, sitting without support was achieved at the age of 8 months, and walking with support started at the of 2 years. She spoke first words at the age of 2 ½ years. At the age of 9, the diagnosis of mild to moderate mental retardation was established. Her personality is very active, curious, and disobedient with affective instability and behavioral abnormalities.

According to the grandmother's information, immunization for BCG, DTP, OPV, and MMR had been administered. The tuberculin skin test was negative.

The **family history** is not complete as the father is unknown. The family is of Gypsy origin. All members of her family were healthy and denied any hereditary condition and consanguinity in the family.

Physical examination revealed normal body temperature (36.8 degree C), pulse (78/min), respiratory rate (18/min), and blood pressure (110/60 mmHg). She appeared small for age and under weight (22.5 Kg, under 5th percentile), 121cm (under 5th percentile). The head had normal shape and contour and head

circumference was normal (50 cm). Ocular examination revealed epicantal folds and narrow palpebral fissures, bilateral lens implantations, amblyopia, strabismus, and horizontal nystagmus. We don't know if the patient had microcornea before the first replacement. These features associated with a long philtrum and malar hypoplasia, are the components of the mild facial dysmorphism. Hearing appeared normal. Nose, mouth and throat did not show any abnormalities. The neck has normal flexibility, but was held in almost permanent anterior flexion (related to amblyopia). The lymph nodes were not palpable.

The spine is normal. The thorax is symmetrical with normal contour and regular, symmetric respiratory excursions. Lungs appeared normal on percussion and auscultation. Cardiac auscultation was normal. No abnormality of the abdomen, liver or spleen was present. Genitalia were normal for age. The skin showed mild hyperpigmentation (owing to the racial background). The extremities were thin and gracile. The neurologic examination: "gait disturbance (uncertain, hesitant) with lateral undirected deviation, hitting the ground with the back of her feet (splashing gait). Peripheral motor syndrome (neuropathy): symmetrical bilateral decreased muscular force in lower limbs; absence of deep tendon reflexes in lower limbs. There were no superficial and deep sensory deficits. The patient cannot walk on her heels. Tremor and involuntary movements of upper limbs and fingers suggest a mild choreoathetosis. The patient presented with poor coordination of upper and lower limb movements (dysdiadochokinesis and abnormal heel-knee-shin test)."

The laboratory data, *during the last febrile episode* (February 2007) revealed anemia Hb 10.4g/dL, Ht 29.8%, MCV 78.4fL, MCH 27.4pg, RBC 3800000/mmc; WBC 8400/mmc; PLT 168000/mmc. The erythrocyte sedimentation rate (ESR) was 68mm, and the C reactive protein (CRP) was 7,35mg/dL; BUN: normal; *hypertransaminasemia: ALT 403u/L (normal <51), AST 496 u/L(normal <39); GGT 18uL (normal<32); CK 10,000uL (normal<229), LDH 2500u/L.* RF: negative; ANA: negative; serum immunoglobulins: IgG 840mg/dL; IgA 66mg/dL; IgM 68mg/dL. Cytomegalovirus (IgM): negative; Epstein Barr virus (IgM): negative; HIV

(1+2 total antibodies): negative; HIV(total antibodies): negative; Cytomegalovirus (IgG): positive. After a week, CK (1400u/L) and LDH (1638u/L) decreased, and also the acute phase reactants: ESR (12mm), CRP (0.05mg/dL). After two weeks, normal values of all these parameters were recorded. ❑

Other investigations

CT with contrast (cranium)/27.12.2004) showed normal ventricular system, no pathologic findings in pericerebral spaces, normal density and contrast enhancement of the supra- and infratentorial parenchyma (including cerebellum). There were no focal lesions.

MRI (cranium)/13.08.2008 (conclusions): Normal range (including cerebellum).

CSF/27.12.2004 was Pandy negative 27 elements/mmc with normal biochemical exam.

Nerve Conduction Velocity (right peroneal nerve): 21.34m/sec (normal>40.0).

Left Sural nerve biopsy: Sensory nerve showing signs of a moderate predominantly demyelinating type neuropathy: 20% of teased fibers were regenerated and presented segmental remyelination lesions, and 3% had segmental demyelination lesions. Discrete signs of axonal degeneration could be observed too: 2% of the teased fibers presented myelinic ovoids and bullae, the myelinic fiber histogram was unimodal with maximum fiber diameter being 8-9 μm in less than 1% of fibers, indicating the predominent involvement of the large myelinic fibers. Myelinic fiber density was practically at a lower normal limit-6790 fb/mm^2 (transverse sections), due to a very intense regenerative activity-33% of teased fibers (13% regenerated fibers + 20% regenerated fibers with remyelinating lesions).

Left Gastrocnemian Muscle Biopsy: minimal nonspecific morphological changes.

Molecular genetic testing: A DNA sample was tested for mutations in the **coding region of the SIL1 gene** (MSS, 5q31). The patient's DNA was found to be wild type for the nine coding exons of the *SIL1* gene. In addition, a partial sequence of intron 6 of the *CTDP1* gene (CCFDN, 18qter) was amplified by PCR and subjected to automated fluorescent sequencing. A homozygous mutation IVS6+389C>T was detected by comparing the patient's

sequencing electropherogram with the wild type sequence. This mutation has been previously shown to result in aberrant splicing and an Alu insertion in the processed mRNA (3). The nucleotide change was confirmed in two independent PCR reactions and sequencing runs (2). All the other members of her family were unaffected and no genotyping was performed. ❑

RESULTS

Two reasons justify our interest in this case. One is that the first descriptor of MSS was a famous Romanian neurologist (1,4,5). The second reason is that CCFDN was described in the Gypsy population, and despite the fact that the Gypsies represent an important ethnic group in Romania, we do not know about previous cases published in our country, except the two case-reports described as MSS with neuropathy in 1983 and 1995 (6,7). It seems that Marinesco's patients were of gypsy origin as well (5). Initially the diagnosis of MSS seemed more appropriate for our patient (bilateral cataracts, ataxia, mental retardation, short stature, pronounced hypotonia, and myopathic (although very minor) changes on muscle biopsy). The presence of others features – facial dysmorphism, peripheral neuropathy, acute para-infectious rhabdomyolysis and Gypsy origin – suggested the differential diagnosis of an MSS variant, such as the CCFDN syndrome recently described in a specific gypsy group from Bulgaria (8-10). CCFDN was also described in many other countries in gypsy population (11,12). This was the reason to solicit molecular genetic testing confirming the diagnosis. ❑

DISCUSSIONS

To date, CCFDN has been found to occur exclusively in patients of gypsy ethnicity (carrier rate: ~ 6-7%); over 100 patients have been diagnosed (8). CCFDN and MSS have some clinical manifestations in common (bilateral cataracts, ataxia, mental retardation, short stature, hypotonia). Major features of MSS that distinguish it from CCFDN are the occurrence of more severe mental retardation marked cerebellar atrophy, and chronic myopathy with specific ultrastructural features on muscle biopsy. On the other hand, CCFDN patients present with demyelinating peripheral neuropathy, facial

dysmorphism, microcornea, and episodes of *myoglobinuria* and rhabdomyolysis (11,13,14).

The diagnostic criteria for CCFDN *include congenital cataracts and microcorneae, primary hypomyelination of the peripheral nervous system, impaired physical growth, delayed early motor and intellectual development, mild facial dysmorphism* (prominent midface with a well-developed nose, thickening of the perioral tissues, forwardly anterior directed dentition and *hypogonadism* (8,10). Except for hypogonadism (the patient is a prepubescent girl!) and facial dysmorphism, all these abnormalities are present in our case. Facial dysmorphism develops in late childhood and is more evident in male patients.

As in our case, the most striking neurological manifestation in CCFDN patients is a symmetric, distally accentuated, predominantly motor peripheral neuropathy. Loss or depression of tendon reflexes, initially in lower limbs, is observed. Nerve conduction velocities are usually reduced in affected children after 18 months. Sensory action potentials values are of normal amplitude, suggesting a relatively uniform degree of slowing of conduction across nerve fibers, consistent with congenital hypomyelination, also provided by nerve biopsy (8,14). Other neurological abnormalities in our patient include choreiform movements and upper limb postural tremor, considered as less consistent in CCFDN). Para-infectious rhabdom-yolisis, also present in our patient (severe myalgia, weakness and massive increased CK and LDH) following a unspecified viral infection, is a serious complication reported in an increasing number of patients (8) and may represent a common environmentally-triggered feature of CCFDN syndrome (8,15). Prenatal eye development is constantly affected and the congenital cataracts are the first CCFDN manifestation, recognizable in early infancy (8). Other ocular abnormalities are microcornea, microphtalmos, micropupils, floppy eyelids, long and dense eyelashes, nystagmus and strabism. Other clinical manifestations include small stature, low weight, mild facial dysmor-phism, cerebral and spinal cord atrophy on neuroimaging, and osteoporosis (8,16).

Concerning the peripheral nerve in-volvement in Marinesco-Sjogren syndrome, we have to mention the electrophysiological observations of *Skre et al* (1976, cited by 6) who

noted neurogenic involvement of the muscle in one case, that of *Fontaine et al* (1974, cited by 6) who observed neurogenic-type electro-myogram and slightly reduced motor cond-uction velocity in one case, as well as that of *Yamanaga et al* (1980, cited by 6) who reported clinical and neurophysiological signs of peripheral neuropathy in 3 patients belonging to the same sibship. On sural nerve biopsy *Hakamada et al* (1981, cited by 6) described segmental demyelination lesions in one patient, and *Alexianu et al* (1983, 1995) reported segmental demyelination with secondary axonal degeneration in 2 patients.

CCFDN is a genetically homogenous condition, where all patients are homozygous for the same ancestral mutation in the CTDP1 gene on chromosome 18qter (3). The *CTDP1* gene encodes a protein phosphatase whose only known substrate is the phosphorylated serine residues of the carboxy-terminal domain (CTD) of the largest subunit of RNA polymerase II (2). RNA polymerase II is responsible for the transcription of protein-encoding genes in eukaryotic cells, and the level of CTD phos-phorylation is considered to be a key mec-hanism for the regulation of gene expression (15). Thus, CCFDN belongs to the small group of "transcription syndromes"and, at present, is the only known defect directly involving RNA polymerase II-mediated gene expression (8).

In early infancy, a differential diagnosis to be considered is galactokinase deficiency, common among the Gypsy ethnics, leading to cataracts in the first weeks of life. Thus, infantile cataracts should prompt molecular genetic analysis of the *GALK1* gene.

Management includes the treatment of cataracts, and rehabilitation for the peripheral neuropathy. CCFDN patients may develop severe and potentially life-threatening complications during anaesthesia (pulmonary edema, inspiratory obstruction, malignant hyperthermia and epileptic seizures). During episodes of rhabdomyolysis may appear potential need for intensive care.

Prognosis. The ophtalmological and neurological abnormalities are not curable but these patients are manageable, allowing an acceptable quality of life and daily activities.

Genetic counselling and prenatal predictive testing for the disease mutation on DNA extracted from chorionic villus samples can be offered to the family. ❑

Conclusion

The case described above is a typically one for CCFDN. This occurrence, usually exceptional, is not so rare in genetically isolated populations like Gypsies.

The mutation in the CTDP1 gene was demonstrated.

The distinction between MSS and CCFDN, suggested by some authors, remains unclear but is quite evident that MSS is clinically and genetically heterogeneous. ❑

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