TRICHO-RHINO-PHALANGEAL SYNDROME ASSOCIATED WITH CONGENITAL CYTOMEGALOVIRUS INFECTION

Ileana Ioniuc, Stela Gotia, Aurica Rugina, M. Colta, Alina Murgu, Monica Alexoae
II Pediatric Clinic, "Gr. T. Popa" Medicine and Pharmacy University, Iasi

ABSTRACT

Tricho-rhino-phalangeal syndrome, disease with genetic determinism, is characterized by abnormal hair growth, facial dysmorphism and skeletal impairment. The evolution of the case is variable according to the three types of the disease. This case is particular by the association with cytomegalovirus infection, the delay in neurologic and cognitive development of the child being affected by both diseases.

Keywords: tricho-rhino-phalangeal syndrome, cytomegalovirus infection, child

INTRODUCTION

Tricho-rhino-phalangeal syndrome (TRPS), a disease with genetic base, is characterized, in most cases, by abnormal hair growth, unusual facial features and skeletal impairment.The disease's name is coming from the latin words hair (tricho), nose (rhino) and phalanges. It has three types, type 1 being the most common. Characteristic facial appearance with a bulbous, rounded nose, thin upper lip, long philtrum, large ears and rare and brittlehair; all children associated short stature. (1) Overlap of oneembriofetopathy to a genetic disease may interact to further development of these patients. Neonatal infection with cytomegalovirus (CMV), one of the most important congenital infections in developed countries, may progress to severe hepatic impairment, neurologic impairment (mental retardation, deafness, ocular and neuromuscular impairment). (2)

CASE PRESENTATION

L.D.S., 4 years old, from rural areas, had multiple hospitalizations for reassessment and treatment in II Pediatrics Clinic, Children's Hospital "St. Maria" from the age of 4 months. The child comes from a young couple, apparently healthy, pregnancy monitoring by the family doctor, normal natural birth, at 38 weeks, size 49 cm, weight 2700 g, without neonatal suffering and without jaundice at birth, natural food for two months. During pregnancy, the mother has not made specific serology tests for transmitted infections (hepatitis, cytomegalovirus or toxoplasma gondii). It has a 1 year old sister apparently healthy.

He was sent to hospital at the age of four months, when this size was 62 cm, weight 5400 g, with a slight psychomotor retardation (difficulty holding head), discrete microcephaly (-1DS), aggravated intentional tremor, convergent strabismus, important hepatocytolisis (227UI/ml TGP, TGO 228 UI/ml) (Figure 1). Serological tests were negative for congenital toxoplasmosis (Toxoplasma gondii Ac anti-IgM and IgG), congenital rubella (rubella virus Ac - negative), hepatitis B and C (AgHBs, AcVHC) and positive for CMV infection (Ac anti CMV IgM and IgG). The exploration scheme for differential diagnosis were considered fetal alcohol syndrome (negative history, normal values of γGT),

Coresponding author:
Dr. Monica Alexoae, "Grigore T. Popa" University of Medicine and Pharmacy, 62 Vasile Lupu str., Iasi
e-mail: m_alexoae@yahoo.com

metabolic hepatitis (glucose, blood and urinary copper l cerulopasmineandα1-antitrypsin with normal values).It been established specific therapy with Ganciclovir (10 mg/kg in 2 divided doses for 14 days) associated with hepatoprotective medication, subsequently vitamin therapy, with favorable evolution of hepatocytolisis syndrome. Cerebral CT examination revealed normal brain substance, fluid spaces with normal appearance, except that the fourth ventricle and aqueduct of Sylvius, that was small. The patient no longer come to hospital, until the age of age of eight months, when clinical examination reveals a mild hypotrophy (G = -1.59 SD, T = -2.25 SD), discrete facial dysmorphism with microcephaly (-2.51 SD) trigonocephaly, convergent strabismus both eyes, slightly psychomotor retardation. Laboratory didn't revealed hepatocytolisis and Ac anti CMV were negative. It raises the suspicion of a genetic syndrome associated with CMV infection, genetic examination underlying the possibility of a genetic disease:tricho-rhino-falangian syndrome type 1; thekaryotype is normal: 46XY.

Reassessed at the age of eight months, and after 12, 18, 24, 30 months: transaminases remained normal, but the disease has evolved with impaired neuropsychological development (head held from 6 months and stood upright unsupported at 9 months, walk alone at almost 2 years old, speech disorders) and significant decrease in visual acuity. At the age of 4 years the child presents (Figure 3):

- Relatively good general condition, without fever.
- Stature 96 cm, weight 14 kg, BMI 16 kg/m^2
- Facial abnormalities: bulbous, rounded nose, small eyelid slits, down implanted ears, microcephaly, cranial perimeter = 46 cm (- 3, 1DS);

FIGURE 1. *L.D.S. – 1 year and 6 months*

- Underrepresented subcutaneous tissue:;
- Slightly hypertonic muscles
- Thorax slightly flared at the base
- Withoutintentional tremor, psychomotor retardation (broad base walk,speech disorders), myopia, normal osteotendinous reflexes.

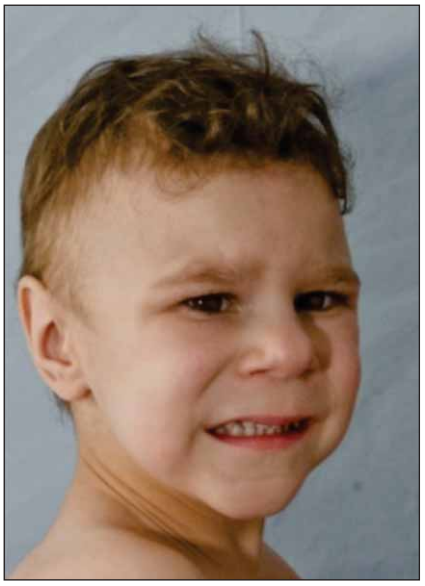

FIGURE 2. *L.D.S. – 4 years old*

Laboratory data revealed normal values for: blood cell count, inflammatory syndrome, transaminases, metabolic investigations and renal function, phosphor and calcium. Osteodensitometry showed normal values for age, both tibial and radial examination; the EEG and EKG and abdominal ultrasound were normal; no modification on upper and lower limbs radiography, normal orthopedic assessment. Neurological and psychiatric examination indicated severe psychomotor retardation with cerebral organic substance; IQ = 50, eye exam - alternating convergent strabismus, myopia.

Diagnosis at this stage remains tricho-rhino-phalangeal syndrome, CMV infection, myopia, alternating convergent strabismus.

Note that each hospitalization for reevaluation were administered B vitamins, neurotrophic medication, cognitive stimulation and physical therapy in specialized services; recommended treatment was done partly at home.

DISCUSSIONS

Tricho-rhino-phalangeal syndrome (TRPS) is a rare disease, mainly, autosomal dominant transmitted, with heterogeneous manifestations, outlining the three subtypes of the disease: type 1 - the most common, type II, been known as Langer – Giedion syndrome and type III - Sugio - Kaji syndrome. Fa-

cial dysmorphism and short stature are the characteristic clinical elements in most cases: prominent nose, thin upper lip, long philtrum, and large ears with rare, brittle hair. (3)

TRPS type I, caused by mutations in the TRPS1 gene, located at chromosome 8 (8q24.12) involve changes of facial features associated with abnormalities of the skin and skeletal abnormalities. Most typical radiological changes are cone-shape epiphyses, mostly at the phalanges. Frequently, these events are not detectable before 2 years of age; bone age is often delayed until puberty. Hip malformations (coxa plana, coxavara) are present in most cases. (2) TRPS type II, based on microdeletions in the TRSP gene on chromosome 8 (8q23.3-8q24.13) but also in other genes - EXT1, is characterized by the development of multiple bony growth (exostoses) (due to EXT1 gene anomalies) and, in most cases, cognitive impairment; microcephaly is observed frequently, may be associated vesicoureteral reflux and repeated respiratory infections; TRPS type III is a more severe form of type I, associated with very small stature, severe brachydactylia due significant shortening of the metacarpal bones, but without exostosis. (3) It been described the association of mental retardation, mainly in patients with TRPS type II, and rarely in patients with type I with important deletions of 8q24; TRSP type I patients with submicroscopic deletions or by point mutations have usually normal intellect. (2) Transmission of the disease is usually autosomal dominant in type I and III and new mutations for type III (3), family risk of having an affected child is 50%.

There is no specific treatment; is necessary to monitor the skeletal and joint damage in conjunction with orthopedic doctor,the vesicoureteral reflux and ophthalmic and auditive functions, orthodontic treatment in some cases, psychotherapy, speech therapy, occupational therapy. (4)Our case was classified into type I in collaboration with the Office of Clinical Genetics Children's Hospital of Iasi.

Cytomegalovirus (herpesvirus family) infection is a very actual issue, with unpredictable developments, especially in young children. Usually, healthy children and adults are asymptomatic, however, in some cases, especially in immunocompromised hosts, can evolve dramatically. Lately, neonatal infection with CMV is involved in a growing percentage ininfants mortality, being one of the most important congenital infections in developed countries. (2).

In the absence of specific treatment (Ganciclovir) and early screening, CMV infection may progress to severe hepatic impairment, sensorineural impairment (mental retardation, deafness, ocular and neuromuscular impairment). The possibilities of disease reactivation require frequent monitoring of these patients (6).

In the presented case, specific treatment applied at the age of 4 months realized normalization of CMV serology and transaminases and good evolution of liver disease, but the CNS disease remains. No activation of the disease was recorded during the period of follow up. The prognosis is influenced by neurologic disturbances already installed and by the association with tricho – rhino – phalangeal syndrome.

CONCLUSIONS

Detection of CMV infection in pregnant women and/or the newborn and early introduction of specific antiviral therapy could improve the prognosis. Co-evolution of disease with genetic determinism complicates the clinical picture of evolution. The presented case is particular by the evolution of early CMV infection in a child with tricho-rhino- phalangeal syndrome. The prognosis is affected by the already installed neurologic, psychologic and sensorial disturbances.

We thank the experts who collaborated in diagnosis and treatment: geneticist Dr. Mihai Voloşciuc, neuropsychiatrist Dr. Laura Ilascu, therapist Dr. Elena Donisa.

REFERENCES

1. **D. Napierala, K. Sam, R. Morello et al.** "Uncoupling of chondrocyte differentiation and perichondrial mineralization underlies the skeletal dysplasia in tricho-rhino-phalangeal syndrome," *Human Molecular Genetics,* vol. 17, no. 14, pp. 2244–2254, 2008
2. **Schleiss M.R.** Persistent and recurring viral infections: the human herpesviruses. *Curr Probl Pediatr Adolesc Health Care***.** Jan 2009; 39(1):7-23
3. **H.J. Lüdecke J. Schaper P. Meinecke, et al**. "Genotypic and phenotypic spectrum in tricho-rhino-phalangeal syndrome types I and III," American Journal of Human Genetics, vol. 68, pp. 81–91, 2001.
4. **M. Gentile, P. Fiorente, A.L. Buonadonna, F. Macina, and F. Cariola,** "A novel mutation in exon 7 in a family with mild tricho-rhino-phalangeal syndrome type I," *Clinical Genetics,* vol. 63, no. 2, pp. 166–167, 2003
5. **Malik T.H., Von Stechow D., Bronson R.T., Shivdasani R.A.** Deletion of the GATA domain of TRPS1 causes an absence of facial hair and provides new insights into the bone disorder in inherited tricho-rhino-phalangeal syndromes. *Mol. Cell. Biol.* 2002; 22:8592–8600
6. **Kimberlin D.W., Lin C.Y., Sanchez P.J., et al.** Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr***.** Jul 2003; 143(1):16-25