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Metabolic syndromes and neural crest development

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Abstract

Aim of this study is to investigate for the possible connection between abnormal neural crest cell (NCC) development and NCC-derived abnormal facial and cerebral structures in 3 children with pyruvate-dehydrogenase (PDH) and in 10 cases with oxidative phosphorylation deficiency diagnosed from the Author by standard laboratory assays [i.e. 3 cases of Kearns-Sayre syndrome (KSS), 2 cases of Leigh syndrome, 1 case of KSS with De Toni-Debrè-Fanconi and rachitis (Berio disease), 1 case of KSS with aortic insuffiency and sub-aortic septum hyperthophy, 3 cases of chronic progressive external ophthalmoplegia]. These patients presented with hyperlactacidemia, hyperpyruvicemia and facial abnormalities, similar to those observed in the fetal alcohol syndrome (a typical neurocristopathy) due to PDH deficiency, down-regulating NCC genes.
The Author hypothesizes that the metabolic defect of scarce energy production is responsible of abnormal NCC proliferation/migration and consequent facial abnormalities.

Introduction

The association of neural crest cell-derived abnormal facial and cerebral structures with metabolic abnormalities was repeatedly reported by us [1]. Our personal experience in the study of cases of pyruvate –dehydrogenase (PDH) and oxidative phosphorylation (OXPHOS) syndromes is reported.

Materials and methods

Chronic progressive external ophthalmoplegia (CPEO) (3 cases), Kearns Sayre syndrome (KSS) (3 cases), KSS with De Toni-Debrè-Fanconi (1 case), KSS with aortic insufficiency and sub-aortic septum hypertrophy (1 case), Leigh syndrome (2 cases), were diagnosed on the basis of laboratory clinical features. Lactic acid, pyruvic acid and amino acids in blood, cytochrome oxidase and PDH were determined by standard methods.

Results

Results are reported in Table 1. All cases presented with facial abnormalities (NCC-derived structures) more important in OXPHOS deficiency syndromes.

Diagnosis	N. of cases	Raised lactic acid and pyruvic acid with L:P<20 (PDH deficiency)	Raised lactic acid and pyruvic acid with L:P>20 (OXPHOS deficiency)	Facial abnormalities
PDH deficiency	3	3		++
KSS	3		3	+++
KSS+De Toni D.F. syndrome	1		1	++++
KSS+aortic insufficiency-subaortic septum hypertrophy	1		1	+++
Leigh syndrome	2		2	+++
CPEO	3		3	+++

Table 1. Facial abnormalities in personal cases of PDH and OXPHOS deficiency.

Discussion

The central neural system starts as a thickeness of the ectodermal midline (the neural plate) induced by two

blocks of mesenchymal cells, present in midline under the neural plate i.e. the notochord and the mesodermal pre-chordal plate [2]. From the latter, signal are sent by the Sonic Hedgehog gene (SHH), which are inductive of the ventral prosencephalon. By Bone morphogenetic protein (Bmp) stimulation of epithelial cells of the dorsal boundary of the neural folds, some cells change from GI to SS state and, after stimulation by the Fgf factor, the Wnt signal and SOX transcription factors, become epithelio-mesenchymal cells of the neural crest (NCC) and migrate [2].

In man, the embryonic stage at which the neural tube is completely formed and NCC migrate is from the 20th to the 55th day of embryonic life, and NCC migrate in three successive streams originating osseous, cartilagineous, vascular and peripheric nervous structures of the face and neck and inducing the formation of the prosencephalon and subsequently of the pallium [2]. The peak neuronal migration to the cerebral hemispheres occurs between the 55th-56th day and the 16th week of gestational age when some heterotopias of the central nervous system are formed [3].

At this time, the cytochrome-c-oxidase (COX), an enzyme of the oxidative phosphorylation (OXPHOS), is present in embryonic cells [4]. Experimental studies in birds and clinical researches in men [2] demonstrated that the embryonic development of the frontonasal-premaxillary structures is connected to the anterior (prosencephalic-diencephalic) neural crest, with subsequent formation of forehead, nasal pyramid, philtrum and superior incisor teeth: the formation of maxilla, lateral teeth, unipolar neuroblasts of III and IV cranial nerve is connected with mesencephalic neural crest. The normal development of the 2nd, 3rd, 4th and first (partially) branchial arch (which contributes to the derma of the ventral part of the neck, the ear lobule, the mesenchyme of the 1st arch, the calcitonine-producing cells of the thyroid gland, the mesenchymal structures of the thymus, the bipolar neuroblasts and somatosensitive and sensorial ganglia of V, VI, VII, IX, X, XI cranial nerves) is connected with the normal development of rhombencephalic neural crests. Once positioned NCC undergo a specific differentiation which requires the activity of transcriptional factors expressed in the ectomesenchyme (Hox, Dlx, Pax, Hand, Pax6, Fox, Sox genes) [2]. In men SHH mutation is the major candidate for fronto-nasal-premaxillary structure malformations [2].

Neurulation disturbance (i.e disturbance of the development and/or migration of NCC) is defined dysneurulation and the anatomical and functional alterations of structures originating from the neural crest cells, following dysneurulation, are defined neurocristopathies. These disturbances may be due to genetic, metabolic (endogenous) and exogenous factors. Some Authors reported the association of OXPHOS disease with developmental anomalies [1,3]. We assumed that OXPHOS deficiency, by virtue of a disturbed oxygen metabolism, may alter face, brain and heart energy production during the critical developmental phase, leading to malformations. Additional genetic or biochemical factors contribute to the pathogenesis of these conditions, leading to complex metabolic and clinical syndromes [1,5,6].

Metabolic syndromes characterized by raised lactic and pyruvic acids in blood with L:P ratio <20 are sometimes due to a PH deficiency. Affected patients, frequently present microcephaly, psychic and somatic developmental delay, dysmorphia (high forehead, broad nose, long or flat philtrum, maxillo-mandibular hypoplasia) i.e. conditions related to disturbances of cephalic neural crest cell proliferation or migration [1].

We observed three familial cases of this condition. One case was a female with facial alterations, epilepsy, language deficiency and L:P ratio = 18. PDH did not showed any alterations, as described in females with x-linked mutations of the PH c E1 alpha subunit [5].

The facial abnormalities observed in these case are similar to those of the fetal alcohol syndrome [5], a typical neural crest disorder, caused in babies by alcohol ingestion by the mother, in which alcohol may inhibit the PDH complex, with secondary PDH defect, fetal hyperlactacidemia and consequent facial abnormalities (as observed in two personal cases).

In other cases, with raised lactic and pyruvic acids, but with L:P ratio > 20, due to OXPHOS abnormalities, we observed similar but more important facial dysmorphia associated with myopathy, cardiac, nervous and endocrinological disturbances. These cases are constitutive of specific clinical syndromes. In CPEO syndrome, characterized by one or more OXPHOS enzyme deficiencies, progressive external ophthalmoplegia and myopathy and in KSS, a pediatric syndrome characterized by external ophthalmoplegia, pigmentary retinopathy and one of these symptoms: ataxia, cardiac blocks, raised proteins in cerebrospinal fluid, the facial dysmorphia is more evident [1].

Three cases of CPEO and 3 cases of KSS were diagnosed by us. One case of KSS is reported here. The female patient showed at birth round face, high forehead, wide nasal bridge, upturned nose, long and flat philtrum, long and thin vermilion border of the upper lip, hypoplastic maxilla, ogival palate, low-set ears with hypoplastic lobule, short neck, structures derived from the cephalic neural crest cells and subsequently, a typical KSS. Muscular biopsy showed ragged red fibers (RRF), cytochrome-c-oxidase (COX) deficiency and a 5.5 kb mtDNA deletion. By analogy with PDH deficiency, congenital or secondary to alcohol ingestion in pregnant women, we expressed the hypothesis that the NCC-derived abnormalities of facial and cerebral structures observed in KSS and CPEO are the expression of antenatal OXPHOS deficiency with hyperlactacidemia in NCC and blood and of a consequent abnormal migration of cephalic NCC [1].

The most severe OXPHOS deficiency syndrome is Leigh syndrome, characterized by mtDNA deletion, or a punctiform deletion of ATPase 6 subunit gene (T8993G; T8993C) or a mutation in the nucleus (NDUFV1, SURF1). In Leigh syndrome, a major role of degenerative processes in abnormal brain development is suggested [5]. In two cases affected by this disease with L:P ratio>35, the same facial dysmorphia noted in KSS and the abnormal brain development were ascribed by us to abnormalities of NCC proliferation and/or migration.

Some patients with OXPHOS deficiency showed a renal tubular disease, characterized by typical facial abnormalities

observed in KSS, raised lactic and pyruvic acids in blood, a typical De Toni-Debré-Fanconi syndrome (glycosuria, hyperaminoaciduria, hyperphosphaturia and vitamin D resistant rachitis) and KSS, an association which in our opinion establishes a single disease [6,7].

We report here on a case of this syndrome. The patient, a female, showed at birth the KSS reported facial anomalies and subsequently, the complex KSS symptoms. Muscle biopsy demonstrated RRF, COX deficiency and extensive mtDNA heteroplastic deletion. Lactic acid in serum was 17.5 (nv 8-16), pyruvic acid was 0.5 (nv0.2-0.3 mg/dl). Glycosuria was present; amino acids in urine were globally raised; phosphates in urine were 0.55 (nv 0.3-0.4) mmol/kg/day. Vitamin D resistant rachitis and osteoporosis were observed, with low stature; this association was defined as a single disease (Berio disease) by Karageorgou (2001) [7] with a specific nosological collocation.

NCC are also involved in the formation of the semilunar aortic valves, of the truncal cardiac cushion, from which arises the mitral valve, of the cardiac conduction system and of the membranous portion of the interventricular septum [8].

In a case of KSS, i.e. a male aged 8 years, we observed the reported facial anomalies, aortic insufficiency and sub-aortic septum hypertrophy, hyperlactacidemia and hyperpyruvicemia and in an other, the facial abnormalities and severe arrhythmias [9] confirming the relationship between OXPHOS disease and NCC derived facio-cardial morphologic development.

In conclusion, we reported here the close relationship between NCC proliferation-migration and PDH and OXPHOS deficiency syndromes. In our opinion, the latter may play a role in the pathogenesis of some metabolic and malformative syndromes.

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