Kearns-Sayre syndrome with facial and white matter extensive involvement: a (mitochondrial and nuclear gene related?) neurocristopathy?

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Abstract

The Authors report on a patient with Kearns-Sayre syndrome, large mtDNA deletion (7/kb), facial abnormalities and severe central nervous system (CNS) white matter radiological features, commonly attributed to spongy alterations. The common origin from neural crest cell (NCC) of facial structures (cartilagineous, osseous, vascular and of the peripheral nervous system) and of peripheral glia and partially of the CNS white matter are underlined and the facial and glial abnormalities are attributed to the abnormal reproduction/migration of NCC. In this view, the CNS spongy alterations in KSS may be not only a dystrophic process (leukodystrophy) but also a dysplastic condition (leukodysplasia). The Authors hypothesize that the symptoms may be related to mtDNA mutations associated to NCC nuclear gene abnormality. *SOX 10* gene may be a nuclear candidate gene, as reported in some case of Waardenburg IV syndrome.

Introduction

Kearns-Sayre syndrome (KSS) is a disease of oxidative phosphorylation (OXPHOS) characterized by onset before 20 years of life, ophthalmoplegia, pigmentary retinopathy, and at least one of the following features: ataxia, heart block, and hyperproteinorachia.[1-8] Facial abnormalities were also reported.[2-5] In this paper, we report on a case with facial and white matter extensive involvement.

Case Report

The mother of the male patient presented with hypothyroidism. The patient was born to unrelated parents by normal delivery. At birth, the patient weighed 3580 g and showed some dysmorphic features: high forehead, broad nasal pyramid, long philtrum, hypoplasia of the maxilla and jaw. In the first months of life, he suffered from emesis. At five years, logopedic treatment was started because he presented difficulty in phonation. Dental malocclusion was treated with a prosthesis. Growth was always defective. At 8 years of life, he showed bilateral palpebral ptosis. Tests performed at this age demonstrated growth hormone deficiency.

Physical examination at 9 years demonstrated facial skin hypochromic areas, cranio-facial dysmorphisms including: high forehead, broad nasal pyramid, long philtrum, maxillary and mandibular hypoplasia, thin Cupid's low, dysodontiasis with dyschromic teeth, facial asymmetry (right>left), bilateral palpebral ptosis, and nistagmus. The patient showed transitory diplopia, mild ataxia, and hypoacusia.

Ophthalmologic examination showed reduced visual acuity: right eye 7/10; left eye 8/10. Slit lamp demonstrated diffuse corneal clouding, dystrophy of the epithelial layer with stromal edema, with appearance of corneal epithelial layer and of Bowman's membrane, *wrought iron* type, and presence of superficial vacuoles, mainly in the nasal field of the right eye and in the temporal field of the left eye. The peripheral visual field was generally constricted.

At 11 years of age, visual acuity had reduced to 3/10 on the right eye and 3-4/10 on the left eye. Hypofunction of medial rectus, lateral rectus, obliquus parvus, superior rectus muscles bilaterally, and major obliquus on the right eye was present, with ophthalmoparesis. Ophthalmoscopic examination showed diffuse bilateral macular and peripheral pigmentary retinopathy. ERG demonstrated normal evoked retinal potentials and defect of retino-cortical transmission and of cortical activation of potentials.

Blood glucose, complete cell count, lactic and pyruvic acid were normal as well as urin analysis, urine levels of amino acids, organic acids, sodium, potassium, chloride. Thyroid hormones and serum were also normal. ECG showed complete right bundle branch block. Echocardiography showed subaortic septum hypertrophy and aortic insufficiency.

On the basis of clinical and laboratory features, diagnosis of

KSS was made. At 13 years of age, the boy presented maculated incisors, hypocalcemia (7.4-7.8 mg/dL), hyperphosphatemia (5.7 mg/ dL; NV 2-5), hypomagnesemia (1.5 mg/dL; NV 2-3), low ionized calcium (o.89; NV 1.19-1.39 mmol/L); in urine, K was 23 mg/day (NV 24-120), chloride 99 mg/day (NV 110-250), calcium 26 mg/day (NV 50-100), phosphates 300 mg/day (NV 500-2000); in serum, parathyroid hormone was normal. Hypomagnesemia and hypoparathyroidism due to ineffective parathormone were diagnosed.

Protein and lactic acid level in cerebrospinal fluid were elevated (1.74 g/L and 2.6 mmol/L, respectively).

On Southern blot, a 7kb mtDNA deletion, heteroplasmic in 60% of lymphocytes was demonstrated.

Audiometry: bilateral neurosensorial hearing loss at high frequencies (70-90 decibel on the right side; 40-10 decibel on the left side above 2000 Hz).

Auditory brainstem response (ABR): normal function of tronco-encephalic pathways; right ear: regular morphology with latency of the most important component: I=1.5 msec; III/3.9 msec; V=6.15 msec; I-V=4.5; left ear: I=1.5 msec; III=3.8 msec; V=4.5: I-V intervals were in the high normal range.

Magnetic resonance imaging

On T2-weighted images, symmetrical hyperintensity of the white matter immediately below cortical area of the cerebral hemispheres and of gyri temporalis; partial hyperintensity of the white matter of cerebellum, thalami, globi pallidi, posterior part of mesencephalon with lamina quadrigemina, substantia nigra, tegmentum pontis, dorsal part of hindbrain (Figure 1). On TI- weighted images, altered signals were present in the same areas, in globi pallidi, and in some areas of the peripheral white matter. The IV ventricle was wide, with vermis, and cerebellar sulci dilatation (due to hypoplasia or atrophy); subarachnoid spaces were wide. In dorsum sellae, red bone marrow was present, with hypophyseal dislocation.

Computed tomography

Low density of the cerebral white matter, mostly in peritrigonal and frontal regions; symmetrical low density of globi pallidi and putamen.

Proton NMR spectroscopy: low N-acetyl-aspartate in white matter; normal on T2-weighted images (expression of mild axonal damage). Diffusion coefficient: high (expression of microstructural alterations) in cerebral areas.

On the basis of clinical, radiological, and laboratory data, the diagnosis of KSS was made. The syndrome was characterized by facial features, extensive involvement of central white matter and peripheral nervous system (PNS), pituitary-parathyroid deficiency, hyperlactic acid in cerebrospinal fluid due to a large mtDNA deletion and OXPHOS deficiency.

Discussion

In the literature, radiological findings in KSS[7,8] showed an encephalopathy with spotty or diffuse symmetrical lesions, presenting high signal on T2-weighted images and low signal or isointensity on T1-weighted images, affecting most frequently the dorsal and/or ventral part of midbrain, bilaterally substantia nigra or red nucleus, globus pallidus, thalamus and brainstem, pons, cerebellar peduncles, and medulla oblongata.[8]

The subcortical white matter of hemispheres also proved to be involved,[8,9] showing, on T2-weighted images, hyperintensity extending to the subcortical U fibers and sparing the periventricular layers.[7] Hyperintensity of the cerebellar white matter is present,[8] frequently associated with mild cortical atrophy and cerebellar atrophy.

All these findings were present in our patient.

These findings are typical of KSS[7-9] and different from those of other mitochonropathies. In some cases, KSS presents a more extensive glia to reach a pattern of leukoencephalopathy, a term which refers to all forms of white matter abnormality, both inherited and acquired, with extensive involvement of the white matter.[10,11] In a few cases, OXPHOS diseases present a pattern similar to that of leukodystrophy,[11,12] i.e. of a progressive inherited demyelinating disorder while in others,[11] they are characterized by a pattern of leukodysplasia with a malformative aspect.

MRI alone cannot differentiate among these conditions.[6,10]

The MRI pattern of our patient was different from that of periventricular leukomalacia consequent to ischemia in premature infants[13] or to ischemia-hypoxia in full term infants,[14] which are prevalent in the periventricular white matter or in cortico-basal ganglia structures respectively. It also differs from the leukodystrophy that follows oligodendrocyte damage in myelin-associated arylsulfatase deficiency, in which the MRI pattern appears early and involves the older white matter, i.e. the periventricular glia.[7]

In KSS, subcortical white matter involvement is primary[9] and, when extending to one or more structures of brainstem, globus pallidus, thalamus, and cerebellum, it is typical of the syndrome.[8]

The MRI pattern corresponds with histological findings, i.e.

Figure 1. Magnetic resonance imaging of the patient in T2 weighted images. Extensive abnormality of the white matter mainly in frontal and parietal lobes. The periventricular white matter is spared.

spongiform encephalopathy, which is constant, widespread and involving both gray and white matter, with a vacuolization of the central nervous system tissue in a sieve-like appearance;[6,7] in some cases, abnormalities of cranial and spinal nerve roots glia (demyelinating radiculopathy) are associated.[15]

Proton-MRI spectroscopy showed low levels of n-acetyl-aspartate in CNS and increased cerebrospinal fluid lactate, which is the expression of prominent oligodendroglial vacuolar changes.[8] Low n-acetyl-aspartate was present in our patient.

KSS is a typical mitochondriopathy.[2,3,6,7,8,15-17] Mitochondrial enzymes are structurally present in early life in the human embryo, even if they become functionally normal only subsequently, often during the fetal and/or postnatal period.[6] In KSS, large mtDNA deletion[16] is the cause of reduced mitochondrial protein synthesis by the reduced tRNA molecules[18] and by the energy production deficiency, with consequent lactic acid accumulation, capillary proliferation, extensive spongiform changes in cerebrum,[1] cerebellum,[1] spinal cord, basal ganglia white matter and brainstem gray and white matter,[7,8] and predominant neuronal loss in cerebrum and cerebellum.[8] CNS demyelination as a less prominent feature[18] and peripheral nerve demyelination[15,17] were reported. Cerebral white matter seems more sensitive to damage and is a primary target of the mitochondrial OXPHOS dysfunction, through a possible direct involvement of the membrane turnover[9] with hypomyelination, mainly during white matter myelination time[6] (first part of second trimester[6] and first postnatal months), when oligodendrocytes are more sensitive to energy failure,[9,15,18] but starting prior to onset of myelination,[9] because all main elements of brain structures are established in the early embryo.[6]

Retinal-cortical transmission delay reported in our patient was the expression of the involvement of optical pathways and subcortical white matter, as demonstrated[18] by MRI. Temporary and brainstem white matter involvement contributed to the neurosensory hearing loss observed in our patients.[15,17]

In other mitochondrial OXPHOS diseases, as in Leigh disease, necroscopic findings were similar, involving also the putamen, sometimes associated with symmetric necrotic areas and features suggestive of developmental disorders or malformations antedating birth.[18-22]

In KSS cases, it is not possible to state if white matter abnormalities are degenerative (leukodystrophies) or if they have a myelinogenesis defect component (leukodysplasia).[6]

Leukodystrophies have been reported in patients with mitochondrial deletions.[12] Leukodystrophies associated with subnuclear *NDUFV I* gene[23] mutation and COX deficiency associated with SURF I mutation were reported.[24]

In *SCO 2* gene (a COX assembly gene) mutation, gliosis and demyelinating sensory-motor neuropathy, associated with craniofacial dysmorphic features, were shown.[25]

Facial abnormalities, due to mtDNA large deletion, were repeatedly reported in KSS,[2-4] and correlated with neural crest cell (NCC) development.[25,26]

NCC are migratory ectomesenchymal cells, which arise at gastrulation[27] from the edge of the neural plate, present a *neural crest gene regulator network*[28] and give rise to diverse cell types, including bone, cartilage, connective tissue of facial structures, and neurons and glia.

The first stage of this network depends on Wnt, Fgf, BMP, Notch/Delta signalling pathways, which lead to neural plate border formation; secreted molecules induce expression of neural plate specifier genes (*Msx, Pax 3/7, Zic 1, Dlx 3/5*). Subsequently, transcription factors (Snai 1/2 (in human SLUG), Fox d3, Twist, Id, Myc, Tfap 2a, Sox 9/10)[28] activate NCC specifier genes: their expression reflects the specification state of the NCC and confers

to NCC the peculiar features (cycle control, epithelial to mesenchymal transition, migration).

The NCC specifier genes regulate expression of effector genes involved in cell cycle control and activate receptors, which give to cells the capacity to respond to environment.[28]

SOX I0 and *FOX D3* are pan-NCC markers; *SLUG*, *OTX*, *DLX*, *MASH*, and *TWIST* are relevant genes in child development; PAX and MSX families are implicated in cranio-facial development.[29,30]

Snai I, Twist, My b, SOX I0 are NCC specifier genes, which presented mutations in some pathological conditions. NCC, which present mitochondria migrate at 20-55 days of embryological life and differentiate in ectomesenchymal cells, forming, once positioned, structures of bone, cartilage, peripheral neural system, in cranio-facies.[31,32] They migrate into the tunica media of the aortic visceral arch, undergo smooth muscle differentiation, and produce elastic fibers.[32,33]

Experimentally, NCC control Fgf 8 expression in the anterior neural ridge (the prosencephalic organizer) and patterning gene expression in prosencephalic and mesencephalic structures and pallial and sub-pallial structure formation,[32,34] the alar and roof plate,[32,34] in which *PAX 3*, an essential gene for NCC, is expressed. In NCC, *PAX 3* controls *MITF, MET, Myo D* genes, but is related to *EDN3, EDNRB, SOX 10* genes.

NCC control Pax 6 transcription factor in pre-glial cells of radial cerebral and cerebellar[35,36] glia and Pax 3 of Schwann cells.[37]

Oligodendrocytes, the myelin producing cells, are the normal fate of NCC;[38,39] in turn, glia give rise to neurons.[40,41] NCC contribute to aortico pulmonary septation.[42] Glia cell abnormalities during development are present.[43] Thank to the inductive activity of the cephalic NCC, that migrated in the subsequent pre-cordal skull base, the superimposed neural tube is transformed into the prosencephalon, which afterwards differentiates into telencephalon and diencephalon.[44] From telencephalon, subcortical GABA-expressing neurons migrate along the radial glia into the neocortex stimulated by *Dlx* mesencephalon gene activity.[45] From the mesencephalon originate the mesencephalon; myelencephalon and subsequently the cerebellum originate from the rhombencephalon as the hindbrain. NCC development and migration to form the neural tube and the facial structures are termed neurulation; the disturbances of neurulation are defined dysneurulations and the diseases due to NCC abnormal development are defined neurocristopathies.

In the absence of NCC normal migration, the neural tube and facies cannot undergo an appropriate differentiation during organogenesis. In the presence of scarce NCC proliferation, the depending organ is hypoplastic (as in Treacher-Collins-Franceschetti syndrome),[46] due to nuclear *TCOF 1* gene mutation. In the presence of mitochondrial OXPHOS diseases, tissue abnormalities or malformations may arise due to metabolic and/or toxic factors,[47] as observed in alcohol-fetal syndrome,[47] in which facial and cerebral abnormalities are predominant.

In KSS, facial dysmorphia[2-5] and CNS abnormalities were previously reported, attributed to NCC abnormal proliferation/migration[5] caused by mtDNA deletion.[2,5]

High forehead, broad nasal bridge, upturned nose and long philtrum present in our patient depend on fronto-nasal structures, derived from the NCC of the abnormal prosencephalic domain. Maxillary hypoplasia and lateral superior teeth are connected to mesencephalic NCC; mandibular hypoplasia and lateral inferior tooth enamel are connected to the first branchial arch, which partially arises from NCC of the rhombencephalic domain.[32] Aortic and subaortic abnormalities derive from the aortic-pulmonary septum, which is NCC-derived.[42]

In KSS, glia abnormality of white and gray matter is constant.[6]

A strict correlation between NCC development and glia has been recently reported.[38-40] NCC are multipotent cells and may differentiate in vitro into neurons and glial cells, after exposure to various agents (Fgf glial growth factor, brain[39] derived neuroblast factor, TGF B1). In rat, oligodendroglia precursor cells, which express SOX 10,[41] after BMP stimulation followed by culture in bFGF, revert to mutipotent CNS stem cells[36,39] and/or may differentiate into stem cells, progenitors of neurons and glia.[37,39] In CNS, gliogenesis follows neurogenesis.[41] Glia originate in three waves of oligodendrocyte progenitor cells, which populate the forebrain in a ventral to dorsal progressive gliogenesis.[41] Oligodendrocytes precursor cells and oligodendrocytes express the CNS glial transcription factor *Sox 10*[41,43] which, with Pax 3, promotes in PNS Schwann cell production.[43] All glial cells of the PNS originate directly from NCC.[43] NCC development is regulated by NCC transcription factors. SOX 10, SNAI I, PAX 3, and other connected, namely OCT 6, C-Rett, Endothelin, PAX 6.[48,49]

SOX 10 is one of the myelin specific transcription factors expressed in glial cells[50] of CNS and PNS and is important for both myelin development and maintenance. SOX 10 is a NCC development regulator.[51,52]

SOX 10 gene is present early in NCC [50,51] and then in CNS and facial derivative structures.[51] Mutations of nuclear NCC genes and in particular of *SOX 10* are responsible of neurocristopathies with facial and glial CNS and/or PNS abnormalities, as observed in Waardenburg syndrome IV, due to a *SOX 10* gene mutation.[50] SOX 10 is an important transcription factor in the development of both NCC cells[51-54] and glial cells in CNS[55] and PNS[53] and of facial NCC-derivatives[51,53] (cartilage, bone, connective tissue). It maintains the individual cell phenotype[51] and it is critical for glial development in CNS,[51] in which *SOX 10*[53] mutation and the consequent oligodendrocyte abnormal function give rise to a *Neural crest syndrome* with developmental dysregulation (prevailing over degeneration) of glia[56] and of Schwann cells, with peripheral neural crest pathology[57] without Hirschsprung disease.[58] SOX 10 functions synergically with Tst-Oct 6 /S CIP protein of the POU domain as transcription modulator in glial[51,57] cells and is essential for NCC differentiation into glia throught cooperation of different structures. In SOX 10 mutation, a relationship with myelin protein abnormality (PLP or PMP 22)[50] has been proposed.[57]

Some cases of neurocristopathies due to *SOX 10* gene-specific modulator mutations, with facial abnormalities, central and/or peripheral nerve system dysmyelination, were[50,56,58] reported, attributed to SOX 10-OCT/6SCIP[51,59,60] and/or to PAX 3 with PO[57] myelin or PLP and[50,52] mitochondrial involvement. Mice lacking PLP show axonal swelling[59] and glia degeneration attributed to dysmielination.[60]

Conclusions

In our case, in which facial, CNS, white matter, and peripheral glial abnormalities were present, *SOX 10* is a candidate gene for white matter abnormalities, in association with mtDNA deletion. It was recently reported that mtDNA genotype may influence nuclear gene expression, as demonstrated in yeast[61] and in patients with methylmalonic aciduria and vitamin B12 impaired synthesis.[62] In the latter cases, mutated mitochondrial gene induces a signal to the nucleus, to activate mtDNA replication.[62] Previously, we proposed KSS as a neurocristopathy, *i.e.* a disease correlated with NCC abnormality on the basis of facial abnormalities. Here, we hypothesize that, in our patient, the associated facial and severe white mat-

ter abnormalities should both be consequent to mtDNA large deletion, causing NCC abnormality, in which *SOX 10* gene may play a role. On this basis, CNS spongy appearance may be not only degenerative (leukodystrophy) but also dysplastic (leukodysplasia).

Alternatively, mtDNA deletion may be responsible, in our KSS case, of facial and glial white matter abnormalities, due to toxic and/or metabolic substance activity on NCC development.

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