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KEARNS-SAYRE SYNDROME "PLUS"

CLASSICAL CLINICAL FINDINGS AND DYSTONIA

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ABSTRACT - We present a boy of eight years of age with symptoms of Kearns-Sayre syndrome (KSS) characterised by ophthalmoparesis, palpebral ptosis, mitochondrial myopathy, pigmentous retinitis, associated to short stature, cerebellar signs, cardiac blockade, diabetes mellitus, elevated cerebrospinal fluid protein concentration, and focal hand and foot dystonia. The skeletal muscle biopsy demonstrated ragged red fibers, cytochrome C oxidase-negative and succinate dehydrogenase-positive fibers. The magnetic resonance imaging showed symmetrical signal alteration in tegmentum of brain stem, pallidum and thalamus. Mitochondrial DNA analysis from skeletal muscle showed a deletion in heteroplasmic condition. The association of dystonia to KSS, confirmed by molecular analysis, is first described in this case, and the importance of oxidative phosphorylation defects in the physiopathogenesis of this type of movement disorder is stressed.

KEY WORDS: Kearns-Sayre syndrome, dystonia, mitochondrial DNA deletion.

Síndrome de Kearns-Sayre "plus": achados clínicos clássicos e distonia

RESUMO - Apresentamos o caso de um menino de 8 anos com quadro de síndrome de Kearns-Sayre (SKS), caracterizada por oftlamoparesia, ptose palpebral, miopatia mitocondrial, retinite pigmentosa, associada a baixa estatura, quadro cerebelar, distúrbio de condução cardíaca, diabetes mellitus, hiperproteinorraquia e distonia focal em mãos e pés. A biópsia muscular demonstrou a presença de fibras tipo "ragged-red", citocromo C oxidase negativas e succinato deidrogenase positivas. A ressonância magnética de cabeça mostrou alterações de sinal simétricas no tegmento das estruturas do tronco cerebral, globo pálido e tálamo. A análise do DNA mitocondrial do músculo esquelético mostrou a presença de deleção em condição heteroplásmica. A associação com distonia, descrita pela primeira vez neste caso de SKS com confirmação molecular, é ressaltada, sendo discutida a importância dos defeitos da fosforilação oxidativa na fisiopatogênese desta desordem de movimento.

PALAVRAS-CHAVE: síndrome de Kearns-Sayre, distonia, deleção DNA mitocondrial.

Mitochondrial defects may play a role in several movement disorders, within the mechanism of neuronal degeneration. The association between defects of the respiratory chain and dystonia has been investigated by a number of authors[1-8]. Dystonia may be present in diverse diseases caused by mutations of mitochondrial DNA (mtDNA), such as in Leigh's disease, determined by point mutation in the coding gene of subunit 6 of the ATP synthase [9], and in Leber's disease associated to dystonia

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determined by mutations in the coding genes of the complex 1 subunits, mainly ND4 and ND6 [10-14], and by point mutation, more recently described, at position 3460 of the mtDNA [15,16]. Alterations in oxidative phosphorylation are associated to other disorders of movement such as in Parkinson's disease, where greater frequency of 4336 mutation was described in the mtDNA, by some authors[2], contributing to the multifactorial aetiology of this disease. Dystonia was also described in progressive encephalopathy with mutation of the fumarase gene [17] and progressive dystonia with optic atrophy of recessive autosomal inheritance, no gene having been located up to the present time [18].

The Kearns-Sayre syndrome (KSS) is a mitochondrial disease characterised by the onset of symptomatology before 20 years of age, with a clinical picture consisting of ophthalmoparesis, palpebral ptosis, pigmentous retinitis, mitochondrial myopathy, and associated to at least one of the following items: defect in cardiac conduction, cerebellar syndrome, increased cerebrospinal fluid (CSF) protein concentration, and diverse endocrinopathies[19].

In this presentation, we have chosen to report on the case of a patient of our casuistic of KSS with peculiar association of dystonia. To the best of our knowledge, this is the first report on this type of association, with molecular analysis, suggesting "KSS plus".

CASE REPORT

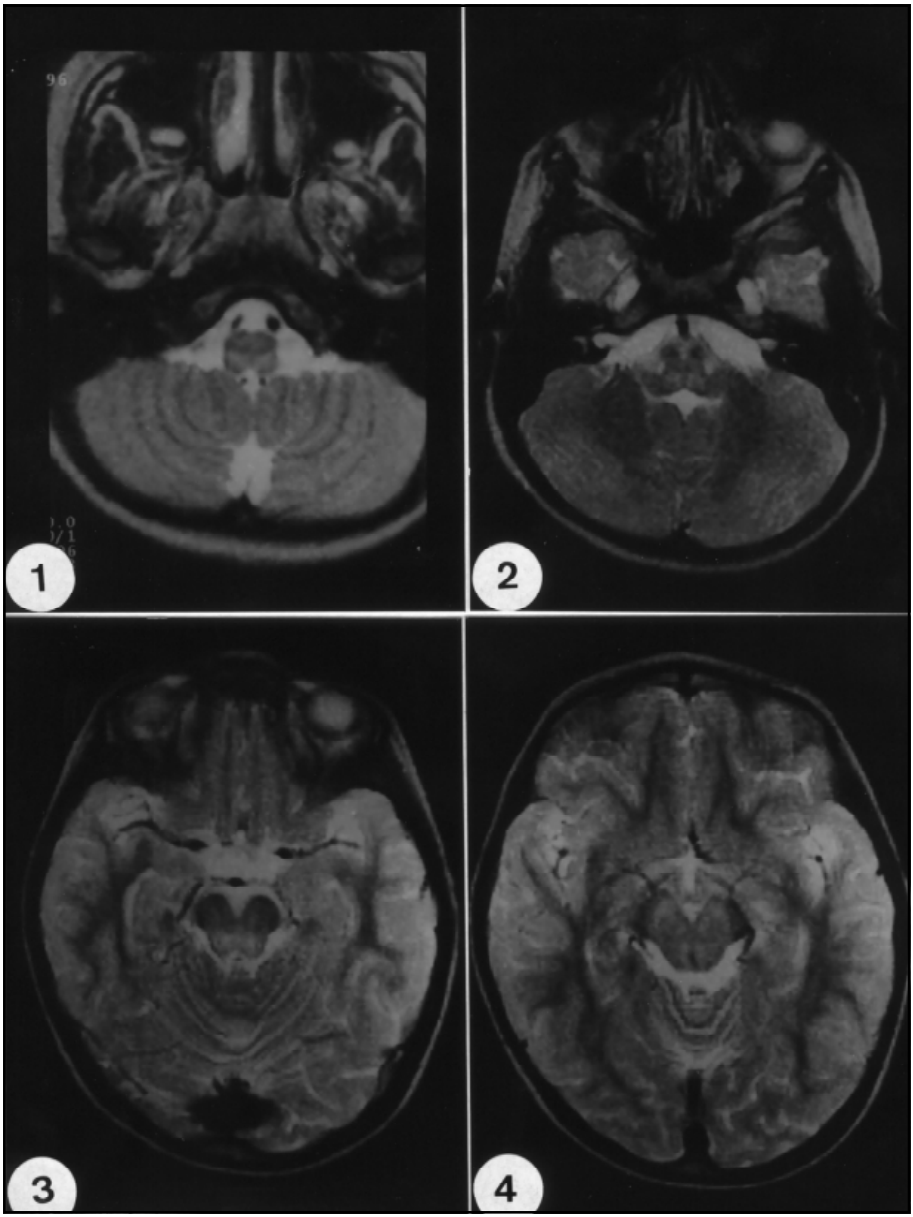
A boy of eight years of age developed ophthalmoparesis and asymmetric palpebral ptosis with complete ptosis on the right as from one year of age. Up to then, he had presented normal neuropsychomotor development, without reference to neo- or perinatal intercurrents. During the seven years of evolution, gradual progressive muscular weakness was observed at the start of proximal predominance evolving to non-sustaining of the cephalic segment and incapacity on deambulation. Dystonia in hands and feet could be observed, characterised by flexion of the fists with fingers outstretched and plantar flexion, with discrete inversion of the feet, accompanied by pain in the hands. Deficient growth in stature was evident, with complaint of loss of balance and difficulty to hold objects.

Clinical examination confirmed short stature, global cerebellar signs, muscular weakness, focal, hand and foot dystonia, pigmentous retinitis, ophthalmoparesis with asymmetric palpebral ptosis, and facial diparesis. Complementary exams showed: cardiac blockade of the right branch, elevated CSF protein concentration (161 mg/dl), threefold increase of the normal value of lactic acid in the CSF and normal serum level of CK, sodium, calcium, phosphorous, magnesium, normal free T4 and TSH, and serum levels of potassium kept to the inferior limits of normality.

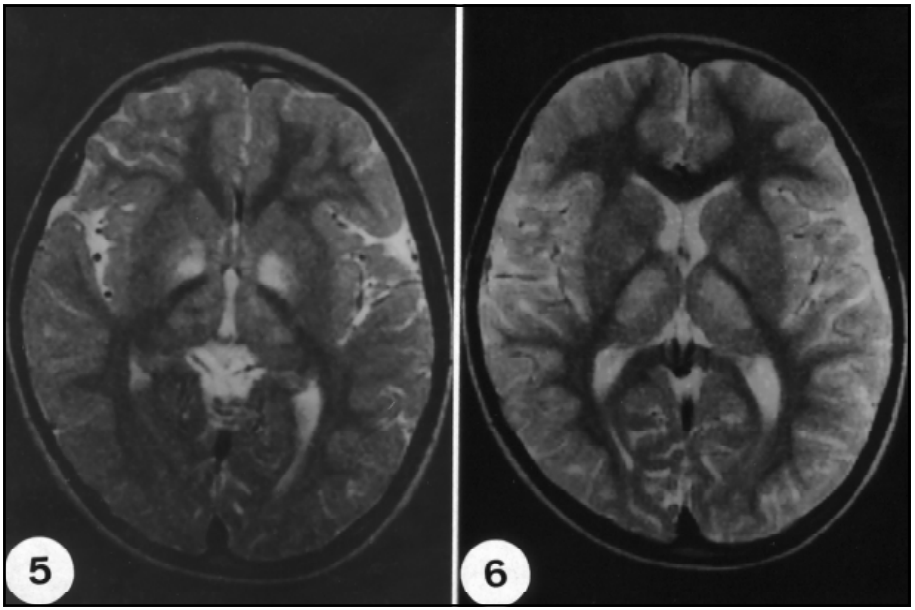
Diabetes mellitus and total inappetence set in during evolution with the need to introduce a gastric probe for food intake. The patient submitted to muscular biopsy of the brachial biceps at 4 years of evolution of the disease (5 years of age), for frozen sections, that showed the presence of 15.2% of the ragged-red fibers (RRF) to modified Gomori trichrome stain, 35% of succinate dehydrogenase-positive fibers, and 19.5% of cytochrome C oxidase (COX)-negative fibers. These histological and histochemical findings confirmed the presence of countless fibers with mitochondrial proliferation, many with COX deficiency, corroborating the hypothesis of mitochondriopathy.

CT-scan carried out at 3 years of evolution (4 years of age) was normal, and the first magnetic resonance imaging (MRI) carried out at 4 years of evolution showed an increase of signal on T2-weighted image in the bulbar level (Fig 1), sparing the *olivaris inferior* complex (Fig 2), pontine and mesencephalic tegmental portion with extension of signal alteration to the substantia nigra (Figs 3-4). An increase signal on T2-weighted image could be observed also in the globus pallidum and thalamus (Figs 5-6). The change was symmetrical and there was no alteration of the signal in the infra- or supratentorial white matter. A second examination of MRI carried out at an interval of one year showed an increase in signal on T2-weighted image in structures of the posterior fossa in the same distribution and extent as on the previous examination. A discrete increase in extension of the hypersignal on T2-weighted image could be observed in the globus pallidus and thalamus, bilaterally, that corresponded to a hyposignal at T1-weighted image. White matter persisted without any abnormality of signal (Figs 7-9).

Suspicion of KSS led to the molecular study of mtDNA. Five micrograms of total DNA extracted from the skeletal muscle and blood were digested with Pvull endonuclease and submitted to electrophoresis in agarose gel at 8%, transferred to a nylon membrane and hybridised with total DNA probe marked with P^{35}. A heteroplasmic condition was observed with the presence of a normal mtDNA band of 16.5 kb and a second band of 10.6 kb, corresponding to a deletion of 5.9 kb. Densitometric study showed the presence of 29.5% of deleted mtDNA in the skeletal muscle, and the deletion was not detected in the blood by the Southern blot method.



Figs 1-4. MRI T2- weighted (2500 TR/ 90 TE) transversal images of 6 mm of thickness, exam performed with 4 years of evolution (5 year-old). 1: slice at the level of medium portion of olivaris inferior *complex showing a symmetrical T2 hypersignal at dorso-lateral portion of bulb, sparing the inferior cerebellar peduncle, and* olivaris inferior *complex. 2: slice at the level of trochlear nucleus showing a symmetrical T2 hypersignal with involvement of* nuclei vestibularis, trigemini, ambiguus, raphes magnus, gigantocellularis, prepositus hypoglossi, *and* solitarius*. 3: slice at the level of intercolicullar area showing a symmetrical T2 hypersignal on the tegmentum with involvement of all grey matter around aqueductus, and the* pars compact *of* substantia nigra*. 4: slice at the level of superior collicullus and the oculomotor nucleus showing a symmetrical T2 hypersignal on tegmentum of mesencephalum with extention to the* nucleus ruber *and* pars reticulata *of substantia nigra.*



Figs 5-6. MRI T2- weighted (2500 TR/ 90 TE) transversal images of 6 mm of thickness, exam performed with 4 years of evolution (5 year-old): show a symmetrical T2 hypersignal on pallidum *and* thalamus, *sparing the internal capsule.*

DISCUSSION

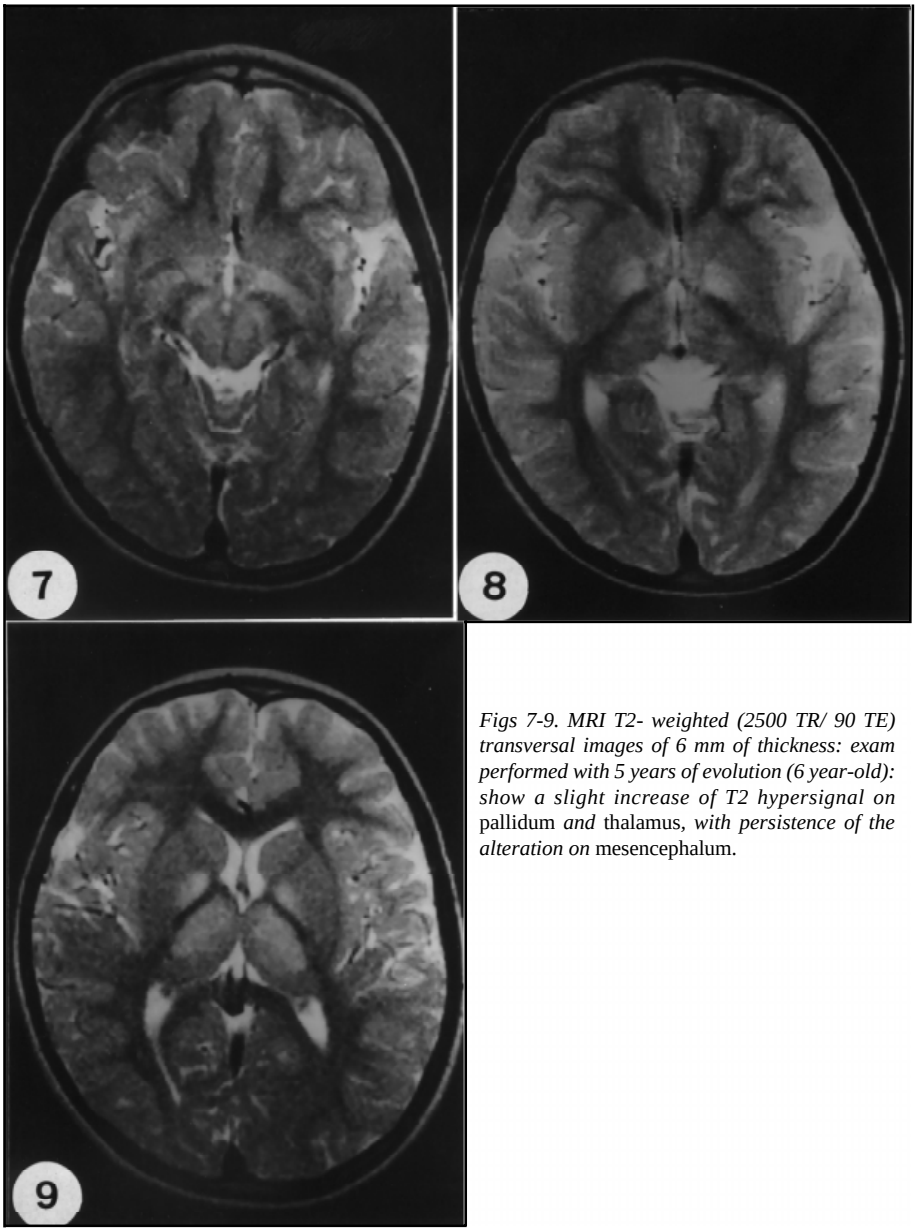
Dystonia may be classified, according to the aetiology, as idiopathic and symptomatic. Ferraz & Andrade [20], in 1992, studied 122 Brazilian patients with dystonic syndrome, of which 37.7% were symptomatic. The most frequent cause was tardive dystonia followed by causes such as perinatal cerebral lesion, cerebral stroke, encephalitis, and Wilson's disease. Mitochondrial cytopathy was cited as one of the less frequent causes.

Leigh's disease and Leber's hereditary optical neuropathy can be considered among mitochondrial pathologies with defects in the respiratory chain that present dystonia. Although some authors [21,22] refer that dystonia is the most frequent manifestation of Leigh's disease, in the study of clinical manifestations of this affection associated to mtDNA point mutations, dystonia was the seventh most frequent manifestation, a match in number to the alterations of the ocular movements[23].

Leber's hereditary optical neuropathy associated to dystonia was described by several authors and is associated to point mutations in the coding genes of complex 1 subunits ND1 [15,16], ND4 [13], and ND6 [11-13], leading to its deficiency, demonstrated by biochemical assays.

The presence of a deficiency of complex 1 in the substantia nigra and in the platelets of patients with Parkinson's disease suggests that defects of phosphorylative chain can occur also in this pathology of movement disorder [3,4,6,24,25]. 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) utilised in the experimental model of Parkinson's disease, involves conversion to 1-methyl-4-phenylpyridinium that inhibits complex 1 in the phosphorylative chain[4].

Recent studies show that the 3-nitropropionic (3-NP) acid, inhibitor of complex II of the respiratory chain, induces a selective neuronal degeneration in the basal ganglia and produces in experimental animals movement disorder characterised by dystonia, chorea, and hypokinesia, similar to the picture of Huntington's disease [26,27]. Alteration of the energetic metabolism of this toxic product



Figs 7-9. MRI T2- weighted (2500 TR/ 90 TE) transversal images of 6 mm of thickness: exam performed with 5 years of evolution (6 year-old): show a slight increase of T2 hypersignal on pallidum *and* thalamus, *with persistence of the alteration on* mesencephalum.

involves the interaction of three processes: disorder in energy production, excitotoxicity, and oxidative stress. The convergence of these three pathways that are co-operative to neurodegeneration may, perhaps, explain the regional selectivity of neurotoxicity in basal ganglia.

Other compounds related to energetic metabolism may also be associated to dystonia. MethylmalonylCoA mutase (MCM) is a mitochondrial homodimer responsible for the isomerization of methylmalonylCoA to succinylCoA. Severe delay or spastic quadriparesis with dystonia was described associated to MCM deficiency [28].

The present case with seven years of evolution, and a picture starting at one year of age, meets the criteria for diagnosis of KSS, presenting dystonia of hands and feet in addition to classical symptoms.

There is a previous description in the literature [29], in 1983, of probable KSS associated to dystonia. The child in this particular description presented ophthalmoplegia, pigmentous retinitis, and disorder in cardiac conduction associated to neurosensorial deafness, torsion dystonia, and myopathy with marked alteration in number, size, and structure of the mitochondria in muscle biopsy. Molecular study was not carried out in this case, for the finding of deletions in the KSS dates from 1988. However, the clinical characteristics are suggestive of KSS, that the authors on that occasion named “ophthalmoplegia plus”.

Episodes of carpopedal spasms interspersed with hypocalcemic generalised tetanus in cases of hypoparathyroidism might enter in the differential diagnosis of the dystonia observed in this patient. Wilichowski et al., in 1997, described four cases of KSS with hypoparathyroidism, with pleioplasmic rearrangement on a broad scale of mtDNA. All four cases described by the authors presented hypocalcemic tetanus with carpopedal spasms [30]. Our patient presented normal serum dosage of calcium and phosphorus, so that the diagnosis of hypoparathyroidism was, therefore, not considered.

The selectivity of affection of the cerebral structures in diseases that proceed with dystonia is starting to be elucidated with the experimental model with 3-NP. Interestingly enough, the structures involved, common to all of these, are: putamen, globus pallidus, and tegmentum of the structures of the brain stem. Our patient presents involvement of the bulbar, pontine, and mesencephalic tegmentum, substantia nigra, globus pallidus, and thalamus, but not of the putamina, in study by MRI. Thalamic involvement was formerly described in KSS [31], in KSS with hypoparathyroidism [30], and in familial dystonia of chronic progress with optic atrophy [32].

The relationship between energetic metabolism and the genesis of the movement disorders, in particular dystonia, are ever clearer. The implication of the defects of complex 1 with dystonia is explicit in Leber’s disease with point mutations in the genes of the subunits of this complex. In the present case, with deletion of 5.9 kb from mtDNA, there was certainly loss of several coding genes of the protein subunits of the respiratory chain. Mapping the deletion with the exact knowledge of the losses may corroborate our discernment and contribute to a better understanding of the physiopathogenesis of dystonia.

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