Neuroradiology (1999) 41: 759–764

B. C. Chu
S. Terae
C. Takahashi
Y. Kikuchi
K. Miyasaka
S. Abe
K. Minowa
T. Sawamura

MRI of the brain in the Kearns-Sayre syndrome: report of four cases and a review

Received: 23 October 1998
Accepted: 8 February 1999

S. Abe · K. Minowa · T. Sawamura
Department of Radiology,
Hokkaido University School of Dentistry,
Sapporo, Japan

B. C. Chu (✉) · S. Terae · C. Takahashi · Y. Kikuchi · K. Miyasaka
Department of Radiology,
Hokkaido University School of Medicine,
Kita-15, Nishi-7, Kita-Ku, Sapporo,
060-8638, Japan
e-mail: chubc@radi.med.hokudai.ac.jp
Tel.: + 81-11-7161161 ext 5977
Fax: + 81-11-7067876

Abstract We report brain MRI findings in four patients with typical Kearns-Sayre syndrome (KSS) and correlate them with clinical manifestations. MRI was interpreted as normal in two patients; cerebral and cerebellar atrophy was seen in the other two. On T2-weighted spin-echo images, two patients had high-signal lesions bilaterally in subcortical white matter, thalamus and brain stem. In one patient, the white matter lesion extended into the deep cerebral white matter and the cerebellum was also affected. The other also had bilateral high-signal lesions in the globus pallidus. There was little correlation between neurological deficits and MRI findings. A review of the literature revealed that 10 of the 13 patients with typical KSS previously studied had bilateral subcortical white-matter lesions on T2-weighted images; at least 7 also had high-signal lesions in the brain stem, globus pallidus, thalamus or cerebellum. Although MRI may be normal or show atrophy, the characteristic finding in KSS is a combination of the high-signal foci in subcortical cerebral white matter and in the brain stem, globus pallidus or thalamus.

Key words Magnetic resonance imaging · Kearns-Sayre syndrome

Introduction

Kearns-Sayre syndrome (KSS) is a rare sporadic multisystem mitochondrial disorder affecting muscle, the central nervous system and endocrine organs. It can cause myopathy, progressive external ophthalmoplegia, pigmentary retinopathy, heart block and/or cardiomyopathy, ataxia, sensorineural hearing loss, mental retardation, growth hormone deficit with dwarfism, hypoparathyroidism, and diabetes mellitus [1]. Abnormal proliferation of mitochondria leading to ragged red fibres (RRF) in the affected muscles may be observed histologically, and can be verified by mitochondrial DNA (mtDNA) analysis [2, 3].

MRI findings in KSS have been reported [4–11]. However, all are based on a relatively small number of cases, and definitions of the disease vary. In addition, correlation with clinical symptoms is ambiguous. We reviewed MRI findings in four consecutive patients with KSS and correlated them with the main clinical features.

Patients and methods

We retrospectively reviewed four consecutive patients with KSS seen from February 1989 to July 1998. They included three females and one male, mean age 19.3 years (range 7–42 years) at the time of the MRI examination. The mean age at onset was 9.3 years (range 3–17 years). The mean interval between onset and MRI was 10.2 years (range 6 months to 25 years). No family history of inherited disorders was found in any patient. All fulfilled the diagnostic criteria of KSS proposed by Moraes et al. [12], i. e. the triad of progressive external ophthalmoplegia (PEO), pigmentary retinopathy and onset before 20 years of age, plus at least one of the following: heart block, cerebellar symp-

Table 1 Clinical findings

Cases	Age	Sex	Onset	PEO	Pigmentary retinopathy	Heart	Cerebellar ataxia	Hearing loss	CSF	RRF	Other findings
1	13	F	10	+	+	–	+	–	Protein ↑	+	Short Stature
2	15	M	3	+	+	IRBBB	+	+	Protein ↑ Lactate ↑ Pyruvate ↑	+	Short stature Hypopituitarism Hypoparathyroidism Hypotonic muscle
3	42	F	17	+	+	–	+	+	Pyruvate ↑	+	Hypotonic and Atrophic muscle
4	7	F	7	+	+	–	–	–	Protein ↑ Lactate ↑	+	IDDM

CSF cerebrospinal fluid, *RRF* ragged red fibres, *IRBBB* incomplete right bundle branch block, + present, – absent, ↑ increased, *IDDM* insulin-dependent diabetes mellitus

toms or cerebrospinal fluid protein levels above 1 g/l (Table 1). We exlcuded both probable KSS (patients with the triad but without other features or patients with an onset after 20 years of age) and patients with PEO and/or ptosis without evidence of multisystem disorders, so as to pursue the manifestations of typical KSS [12]. Through muscle biopsy, it was confirmed that all patients had RRF with modified Gomori trichrome staining.

MRI was performed on a 1.5-T unit using a standard head coil. T1-, proton-density and T2-weighted spin-echo axial images were reviewed by three neuroradiologists (S.T., C.T., S.A.) together. Cerebral and/or cerebellar atrophy and abnormal signal intensity on T1- and T2-weighted images were recorded according to the distribution of lesions in the cerebral white matter, brain stem, basal ganglia, thalamus and cerebellum. White matter lesions were subdivided into subcortical, deep and periventricular.

Results

The findings are summarised in Table 2. MRI revealed cerebral and cerebellar atrophy in two patients (cases 1 and 2), both with cerebellar ataxia. However, another patient with cerebellar ataxia (case 3) had no cerebellar atrophy.

MRI showed white matter high-signal foci on T2-weighted images in two patients. One (case 1) had diffuse, symmetrical bilateral lesions extending from the subcortical to the deep white matter of the cerebral hemisphere, and in the cerebral peduncles, tegmentum of the midbrain and periaqueductal area, superior cerebellar peduncles and cerebellar white matter adjacent to the dentate nuclei. Mildly increased signal was also seen bilateraly in the thalamus (Fig. 1). On T1-weighted images, the lesions were isointense with white matter and could not be detected.

The other patient (case 2) had bilateral lesions in subcortical white matter, and symmetrical lesions in the brain stem, globus pallidus, and thalamus. The brain stem lesions involved the tegmentum of the midbrain, red nucleus, superior cerebellar peduncle, the dorsal part of the pons and the medulla oblongata (Fig. 2). These lesions gave lower signal than grey matter on T1-weighted images.

Reviews of the literature disclosed MRI findings in 13 patients with typical KSS who fulfilled the diagnostic criteria [12] (Table 3). We excluded the incomplete types of KSS from our review. Of the 13 patients with typical KSS, two were older than 37 years and had no abnormal signal in the brain [7]; they had only brain atrophy. The remainder of the patients were less than 30 years old and had high-signal lesions in the cerebral white matter on T2-weighting. Ten patients also had bilateral high-signal subcortical white matter lesions; at least seven also had lesions in both brain stem and basal ganglia. The basal ganglion lesions involved the globus pallidus in six patients and caudate nuclei in two; six patients with brain stem and basal ganglion lesions, bilateral thalamic lesions. In two patients, the white matter lesions were absent on initial MRI examinations but became apparent 2 and 6 years, respectively, thereafter [10, 11].

Discussion

KSS is a mitochondrial disorder with variable definitions depending upon resources [12–16]. Inconsistency in the definition may be related to the variable phenotypic expression of the mitochondrial DNA (mtDNA) genomes, which are transmitted by maternal inheritance [8, 14]. Because most patients with KSS are sporadic, mtDNA deletions are thought to arise by spontaneous mutation in the ovum or zygote. The mutation will then be passed to subsequent generations of cells in a random manner: some cells will have normal genomes (normal

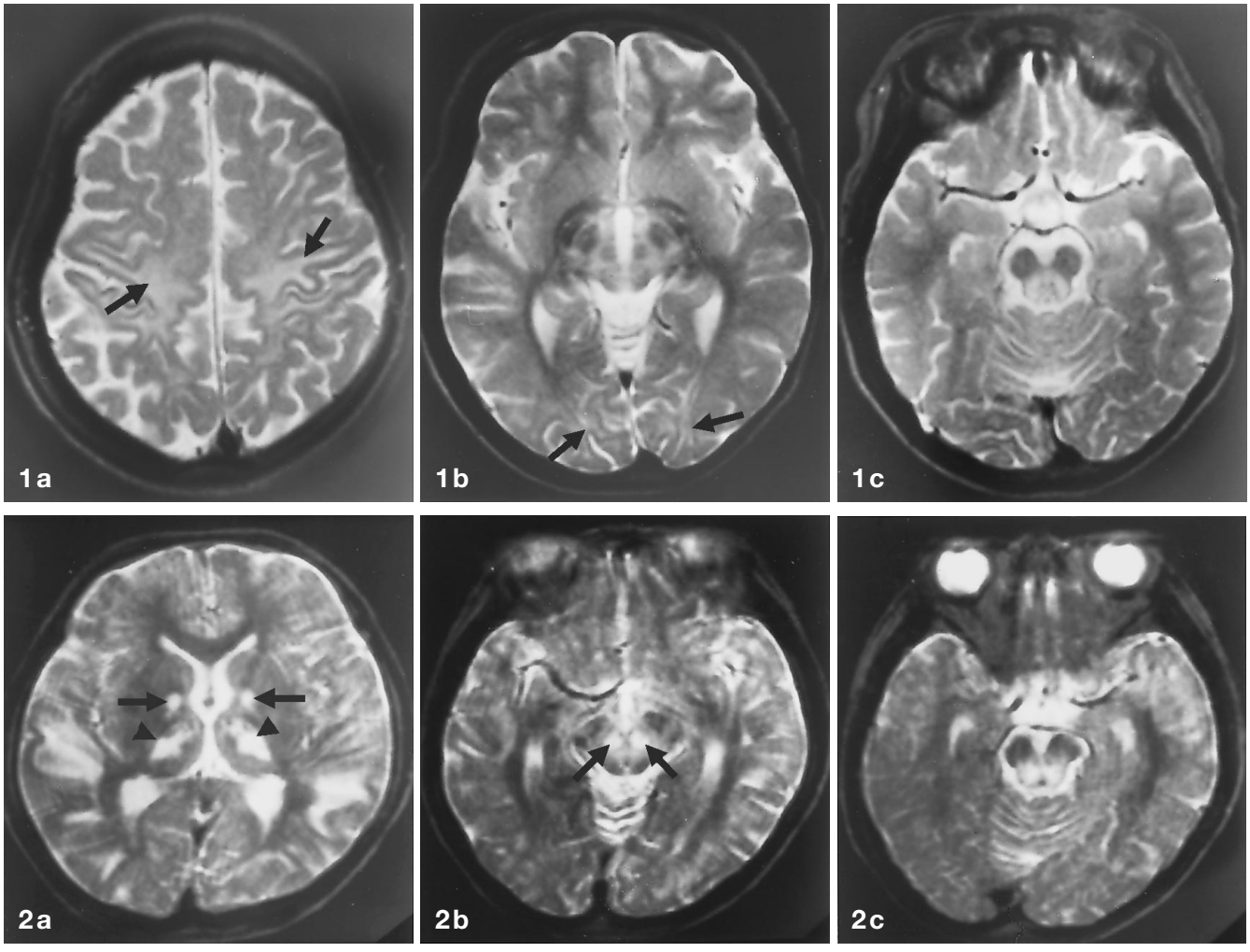

Fig. 1a–c Case 1. T2-weighted axial images demonstrate bilateral high-signal lesions in **a** subcortical and deep cerebral white matter *(arrows),* **b** parietooccipital white matter *(arrows)* and midbrain, **c** mesencephalic tegmentum and superior cerebellar peduncles

Fig. 2a–c Case 2. T2-weighted axial images demonstrate bilateral high-signal lesions in **a** the globus pallidus *(arrows),* thalamus *(arrowheads)* and temporoparietal subcortical white matter and **b,c** in the red nucleus *(arrows),* mesencephalic tegmentum and subcortical white matter

homoplasmy), some a mixed population of mutant and normal genomes (heteroplasmy), and some predominantly mutant genomes (mutant homoplasmy). Differential organ involvement can be explained by mtDNA heteroplasmy in the stem cells of different tissues, and the different thresholds of the tissues for phenotypic expression [3, 12, 14]. We included only patients with typical KSS because the frequency and severity of central nervous system involvement may differ between complete and incomplete forms.

The diagnosis is most convincingly established by a combination of consistent clinical, radiological, pathological, biochemical and molecular abnormalities. A muscle biopsy is one of the early steps in the diagnostic process. This reveals RRF with modified Gomori trichrome stain [16], which all our patients had. We did not review CT studies, although CT may show cortical and white matter atrophy, low density in the cerebral and cerebellar white matter and variable low density or calcification in the basal ganglia, thalamus and/or cerebral hemispheres [5, 17].

We found the following in our study and literature review: normal appearances; cerebral and cerebellar atrophy; and high-signal lesions on T2-weighted images in the subcortical white matter with or without symmetrical involvement of one or more of the brain stem, globus pallidus, thalamus and cerebellum. When we combine the findings in our patients and those in the literature, patients over 37 years old had cerebral and cerebellar atrophy without abnormal parenchymal signal or normal MRI, whereas 13 of 14 younger patients

Table 2 MRI findings

Cases	Atrophy		Abnormal high signal on T2-weighted images				
	Cerebral	Cerebellar	Cerebrum	Brain stem	Basal ganglia	Thalamus	Cerebellum
1	+	+	Bilateral subcortical to deep white matter	+	–	Bilateral	Bilateral
2	+	+	Bilateral subcortical white matter	+	Bilateral[a]	Bilateral	–
3	–	–	–	–	–	–	–
4	–	–	–	–	–	–	–

[a] globus pallidus

had high-signal lesions on brain MRI. Although variable individual brain tissue susceptibility to the mtDNA mutation might account for this difference, further histological and biochemical evidence is needed to elucidate the relationship between age and brain involvement.

The site of brain stem involvement varied. The dorsal and/or ventral parts of the midbrain were involved. The substantia nigra and/or red nucleus were involved in one of our four patients and in two of the 13 in the literature. The cerebellar peduncles, pons and medulla oblongata were also involved in two of our patients, and at least three of the reported patients. The globus pallidus and thalamus were frequently involved [5–8], with high signal on T2- and low signal or isointensity on T1-weighted images.

The MRI findings correspond well with spongiform encephalopathy. Spongy degeneration most frequently affects the cerebral [13, 19–22] and the brain-stem [13, 18–20, 22, 23] white matter. The brain-stem grey matter, including the substantia nigra and red nucleus may also show neuronal loss [20, 22]. Basal ganglia and thalamus can be affected by spongy degeneration [18, 20], neuronal loss and gliosis [19]. The cerebellum and the cervical spinal cord may be affected by spongy degeneration [13, 18–20, 22]. In the cerebellum, loss of Purkinje cells is common [19]. Two of our patients were similar to the case reported by Horwitz and Roessmann [18], in that sponginess was marked in the subcortical zones focally involving the deeper cortical layers, prominent in the globus pallidus and thalamus, and extended throughout the tegmentum of the medulla oblongata. Vacuolisation was intense in the red nucleus and substantia nigra [18].

Correlation of PEO with brain-stem involvement is important because PEO is specifically associated with mtDNA deletions, and is therefore a prerequisite for KSS [12]. However, this correlation seems complex. Some workers reported close correlation and suggested that MRI abnormalities increase with neurological progression [24], while others think that abnormalities on MRI often do not correlate with specific deficits [7, 11]. It has been suggested that brain-stem involvement may be part of the neurogenic origin of the external ophthalmoplegia, in addition to the primary defect of the extraocular muscles [10]. On the other hand, the mitochondrial content of normal human extraocular muscles is high [12], and retrograde degeneration of nerves and nuclei subserving myopathic ocular muscles has been demonstrated in cases with predominantly muscular neuropathological changes [22]. In our study, two patients with PEO showed no abnormality in the brain stem. Therefore, primary abnormalities in the extraocular muscles may be more relevant than brain-stem involvement to the pathogenesis of PEO.

The auditory system includes the organ of Corti, the ventral and dorsal cochlear nuclei, the superior olivary complex, the nucleus of the trapezoid body, the nucleus of the lateral lemniscus, the medial geniculate body, the gyri temporales transversi and tracts connecting these nuclei and gyri. Any involvement of these structures may be responsible for sensorineural hearing loss. Of the two patients with sensorineural hearing loss (inner-ear dysfunction on otology), one had normal brain MRI and the other (case 2) had temporal white matter and brain-stem involvement. Thus, we found little correlation between sensorineural hearing loss and MRI. In the literature, deafness was attributed to virtually total destruction of the organ of Corti in an autopsied patient [19]; inner ear involvement might thus be more contributory than brain lesions to the pathogenesis of hearing losses [25].

Some correlation between ataxia and MRI findings was seen in two of our ataxic patients: both had cerebellar atrophy and one had cerebellar white matter involvement. This result was consistent with the report by Wray et al. [7]; however, in another ataxic patient, MRI appeared normal. Similarly, despite marked cerebellar signal change, ataxia may be absent [24]; MRI signal change need not indicate dysfunction. In KSS, there may be little correlation between cerebellar ataxia and MRI findings.

Proton MR spectroscopy has showed an extreme increase in cerebral lactate and a large decrease in *N*-acetylaspartate (NAA) in KSS, suggesting a metabolic correlate of the prominent oligodendroglial vacuolar changes [26]. This sets KSS apart from amino and or-

Table 3 MRI findings reported in literature

Case, age, (years), sex	Atrophy		High signal on T2-weighted images				
	Cerebral	Cerebellar	Cerebral white matter	Cerebellar white matter	Brain stem	Basal ganglia	Thalamus
1/11/male [4]	–[a]	–	Bilateral, periventricular, patchy	Bilateral	–	–	–
2/6/male [5]	?[b]	?	Bilateral, around central sulcus	Bilateral[c]	Superior cerebellar peduncle and substantia nigra, bilateral	Globus pallidus, bilateral	Ventrolateral nucleus, bilateral
3/9/female [6]	?	?	Bilateral, subcortical and centrum semiovale	–	Bilateral cerebral peduncles, substantia nigra, periaqueductal	Globus pallidus, bilateral	–
4/61/female [7]	+[d]	+	–	–	–	–	–
5/23/male [7]	+	+	Bilateral, subcortical	–	Dorsal	Head of caudate nucleus	Bilateral
6/38/male [7]	+	+	–	–	–	–	–
7/13/? [8]	?	?	Subcortical	+	Dorsal	Globus pallidus, bilateral	Bilateral
8/18/? [8]	?	?	Subcortical	+	Dorsal	Globus pallidus, bilateral	Bilateral
9/17/male [9]	?	?	Bilateral, involving subcortical	?	?	?	?
10/14/male [9]	?	?	Bilateral, involving subcortical	?	?	?	?
11/28/male [9]	?	?	Bilateral, involving subcortical	?	?	?	?
12/9/male [10]	?	?	–	–	Midbrain, pons, medulla	Globus pallidus, bilateral	Bilateral
12/11[e]	?	?	Bilateral, subcortical	Bilateral	Midbrain, pons, medulla	Globus pallidus, bilateral	Bilateral
13/7/female [11]	–	–	–	–	Pons, tegmentum	Globus pallidus, caudate nucleus	Bilateral medial nuclei
13/13[e]	?	+	Deep, sparing periventricular Partial subcortical involvement	+	Dorsal, medulla	Globus pallidus, caudate nucleus, bilateral	Bilateral medial and posterior nuclei

[a] Absent
[b] Not known
[c] Dentate nucleus
[d] Present
[e] Repeat examination

ganic acidopathies such as Canavan's disease, in which a high concentration of NAA can be demonstrated in the brain substance [1]. Although this spectroscopic finding may be a useful sign of mitochondrial disease [8], it is nonspecific, since it may also be seen in tumours, neuroaxonal dystrophy, Cockayne's disease and infarcts.

Although the limited correlation between neurological deficits and MRI findings seems to limit the usefulness of MRI as a diagnostic modality in KSS, primary involvement of the subcortical white matter differentiates KSS from most lysosomal and peroxisomal disorders, in which the subcortical region is affected only late in the process [1]. In young adults or children, the combination of involvement of subcortical white matter and one or more of the brain stem, globus pallidus and thalamus on MRI is highly characteristic of KSS. However, as spongiform degeneration may also be seen in infantile spongy dystrophies such as Leigh's and Canavan's diseases [16], the MRI finding alone is not pathognomonic. Follow-up MRI may be useful in assessing progression of the disease, as shown by Nakagawa et al. [10] and Valanne et al. [11], who demonstrated that white matter lesions appeared after deep grey matter lesions.

References

1. Kendall B (1992) Disorders of lysosomes, peroxisomes, and mitochondria. AJNR 13: 621–653
2. Lestienne P, Ponsot G (1988) Kearns-Sayre syndrome with muscle mitochondrial DNA deletion. Lancet i: 885
3. Shanske S, Moraes CT, Lombes A, Miranda AF, Bonilla E, Lewis P, Whelan MA, Ellsworth CA, DiMauro S (1990) Widespread tissue distribution of mitochondrial DNA deletions in Kearns-Sayre syndrome. Neurology 40: 24–28
4. Elsas T, Rinck PA, Isaksen C, Nilsen G, Schjetne OB (1988) Cerebral nuclear magnetic resonance (MRI) in Kearns syndrome. Acta Opthalmol 66: 469–473
5. Demange P, Gia HP, Kalifa G, Sellier N (1989) MR of Kearns-Sayre syndrome. AJNR 10: S 91
6. Shian WJ, Chi CS, Mak SC (1996) Neuroimage in infants and children with mitochondrial disorders. Acta Paed Sin 37: 96–102
7. Wray SH, Provenzale JM, Johns DR, Thulborn KR (1995) MR of the brain in mitochondrial myopathy. AJNR 16: 1167–1173
8. Barkovich AJ, Good WV, Koch TK, Berg BO (1993) Mitochondrial disorders: analysis of their clinical and imaging characteristics. AJNR 14: 1119–1137
9. Nakagawa M, Tokimura M, Kuriyama M, Higuchi I, Osame M (1991) Chronic progressive external ophthalmoplegia (CPEO): mitochondrial and deletion, brain MRI and electrophysiological studies. Rinsho Shinkeigaku 31: 981–986
10. Nakagawa E, Hirano S, Yamanouchi H, Goto Y, Nonaka I, Takashima S (1994) Progessive brainstem and white matter lesions in Kearns-Sayre syndrome: a case report. Brain Dev 16: 416–418
11. Valanne L, Ketonen L, Majander A, Suomalainen A, Pihko H (1998) Neuroradiologic findings in children with mitochondrial disorders. AJNR 19: 369–377
12. Moraes CT, DiMauro S, Zeviani M, Lombes A, Shanske S, Miranda AF, Nakase H, Bonilla E, Werneck LG, Servidei S, Nonaka I, Koga Y, Spiro AJ, Brownell AKW, Schmidt B, Schotland DL, Zupang M, DeVivo DC, Schon EA, Rowland LP (1989) Mitochondrial DNA deletions in progressive external ophthalmoplegia and Kearns-Sayre syndrome. N Engl J Med 320: 1293–1299
13. Kearns T, Sayre G (1958) Retinitis pigmentosa, external ophthalmoplegia, and complete heart block. Arch Ophthalmol 60: 280–289
14. DiMauro S, Bonilla E, Lombes A, Shanske S, Minetti C, Moraes CT (1990) Mitochondrial encephalomyopathies. Neurol Clin 8: 483–506
15. Wallace D (1992) Mitochondrial genetics: a paradigm for aging and degenerative diseases? Science 256: 628–632
16. Becker LE (1992) Lysosomes, peroxisomes, and mitochondria: function and disorder. AJNR 13: 609–620
17. Seigel RS, Seeger JF, Gabrielsen TO, Allen RJ (1979) Computed tomography in oculocraniosomatic disease (Kearns-Sayre syndrome). Radiology 130: 159–164
18. Horwitz S, Roessmann U (1978) Kearns-Sayre syndrome with hypoparathyroidism. Ann Neurol 3: 513–518
19. Oldfors A, Fyhr IM, Holme E, Larsson NG, Tulinius M (1990) Neuropathology in Kearns-Sayre syndrome. Acta Neuropathol 80: 541–546
20. Clark DS, Myerburg RJ, Morales AR, Befeler B, Hernandez FA, Gelband H (1975) Heart block in Kearns-Sayre syndrome. Chest 68: 727–730
21. Bresolin N, Moggio M, Bet L, Gallanti A, Prelle A, Nobile-Orazio E, Adobbati L, Ferrante C, Pellegrini G, Scarlato G (1987) Progressive cytochrome c oxidase deficiency in a case of Kearns-Sayre syndrome: morphological, immunological, and biochemical studies in muscle biopsies and autopsy tissues. Ann Neurol 21: 564–572
22. Daroff RB, Solitare GB, Pincus JH, Glaser GH (1966) Spongiform encephalopathy with chronic progressive external ophthalmoplegia. Central ophthalmoplegia mimicking ocular myopathy. Neurology 16: 161–169
23. Groothuis DR, Schulman S, Wollman R, Frey J, Vick NA (1980) Demyelinating radiculopathy in the Kearns-Sayre syndrome: a clinicopathological study. Ann Neurol 8: 373–380
24. Kapeller P, Fazekas F, Offenbacher H, Stollberger R, Schmidt R, Bergloff J, Radner H, Fazekas G, Schafhalter-Zoppoth I (1996) Magnetic resonance imaging and spectroscopy of progressive cerebral involvement in Kearns-Sayre syndrome. J Neurol Sci 135: 126–130
25. Weidauer H, Lenarz T (1984) Kearns-Sayre syndrome from the otorhinolaryngologic viewpoint. (In German) Laryngol Rhinol Otol (Stuttg) 63: 141–146
26. Matthews PM, Andermann F, Silver K, Karpati G, Arnold DL (1993) Proton MR spectroscopic characterization of differences in regional brain metabolic abnormalities in encephalomyopathies. Neurology 34: 2484–2490