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J C Allard, S Tilak and A P Carter

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CT and MR of MELAS Syndrome

Jeffrey C. Allard,^{1,2} Shripad Tilak, and Anthony P. Carter

MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke) syndrome was first described in 1984 by Pavlakis et al. [1] after reporting three cases of their own and identifying eight others in the literature. Although MELAS syndrome shares some similarities with Kearns-Sayre syndrome and MERRF (myoclonus epilepsy and ragged-red fibers) syndrome, they believe it to be a distinct clinical syndrome, and it is generally accepted as such [2]. All three syndromes are similar in that ragged-red fibers are found on skeletal muscle biopsy, indicative of a mitochondrial abnormality, and that spongy degeneration is found in the brain. Clinically similar features include short stature, dementia, weakness, sensorineural hearing loss, and serum lactic acidosis [3]. Features that clinically differentiate MELAS are presence of cortical blindness and hemiparesis, and absence of ophthalmoplegia, heart block, and myoclonus [3].

Perhaps because this is a rare and complex neurologic syndrome, most of the literature has focused on the clinical and biochemical abnormalities. Unfortunately, the radiologic descriptions have been brief and the image quality of the few published CT scans has been poor [1]. Of the original 11 cases of MELAS syndrome reported, six had CT scan results recorded and we identified two subsequent cases [4, 5] in the literature in addition to the two we describe here, enabling us to review the CT findings in 10 patients as well as the MR findings in two. CT in the two cases reported here was performed on various scanners and MR was performed on a 0.15-T prototype magnet.*

Case Reports

Case 1

The patient was short, had healthy parents, but was noted to do poorly in school beginning at about age 7. At age 9 he was found in a postictal state but subsequent neurologic examination was normal and no treatment was given. Several months later, cortical blindness developed and complex partial seizures became more frequent. A progressive downhill course in motor and cognitive function was noted. A CT scan with contrast at age 10 showed multiple hypodense lesions especially in the left occipital lobe and right parietal lobe, with gyral enhancement to the latter (Fig. 1A). Encephalitis and vasculitis were considered. Because *Toxoplasma* titers were elevated, the patient was treated but failed to improve. He became totally demented and quadriplegic.

At age 12 the patient had a CT scan without contrast that showed significantly increased atrophy with focal hypodense areas in both cerebral hemispheres, especially the parietooccipital regions (Fig. 1B). A brain biopsy showed a perivascular inflammatory process (mononuclear cell infiltrate) that was consistent with an inflammatory process but not with vasculitis. There was no response to steroids. Reevaluation at age 14 finally led to the correct diagnosis when serum lactic acidosis was noted. Review of the brain biopsy showed evidence of scattered vacuole formation consistent with spongy degeneration. The mononuclear cell infiltrate could have been explained on the basis of reactivity to necrotic brain tissue. MR images best demonstrated the abnormality on T2-weighted images, which showed high signal in the involved gray and white matter lesions, especially in both cerebellar hemispheres and occipital lobes (Figs. 1C–1F).

Case 2

This short fireman was well until a progressive bilateral sensorineural hearing loss was documented at age 23. At age 27 he was admitted with headache and left homonymous hemianopsia. A CT scan showed basal ganglia calcification and hypodensity in the righ parietooccipital region. The working diagnosis was complicated migraine.

At age 28 he presented with a fluent aphasia, confusion, and right hemiparesis. A CT scan at this time showed a new hypodense region in the left temporoparietal region. Four-vessel angiography showed questionable slow flow to scattered areas in the late arterial phase that was thought to be consistent with the clinical diagnosis o "atypical vasculitis." Proteinuria was noted and a renal biopsy was consistent with glomerulonephritis, which resolved with steroid ther apy.

At age 29 focal and generalized seizures began. By age 30 disorientation and generalized neurologic deterioration required that he be placed in a nursing home. His latest admission at age 31 was for increasing seizures, headache, and ataxia. EEG showed a seizure focus in the left parietal lobe, and medications were altered. The

^{*} Field Effects, Acton, MA.

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¹ All authors: Department of Radiology, Neuroradiology Section, Boston University and Boston City Hospital, 818 Harrison Ave., Boston, MA 02118. Address reprint requests to S. Tilak.

² Present address: Department of Radiology, Mount Sinai Medical Center, 4300 Alton Rd., Miami Beach, FL 33140.

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Fig. 1.--A, CT scan with contrast shows gyriform enhancement pattern to right parietal lobe with central hypodensity. Smaller areas of focal atrophy are noted in right anterior frontal, left frontal, and left parietal lobes. B, CT scan without contrast 3 years later shows marked atrophy, with dilatation of the right occipital horns greater than the left. Scattered hypodense

areas are noted in cortex and region of basal ganglia.

C, Axial spin-echo MR image (1500/100) shortly after CT in Fig. 1B shows diffuse cerebellar involvement.

D, Note volume loss with scattered high-signal areas in left temporal lobe. There is extensive high signal in both occipital lobes and in quadrigeminal plate, but sparing of the brainstem.

E, High-signal areas are present in occipital and temporal lobes. Also note involvement of lentiform nuclei and thalami.

F, Largest abnormality is in left parietal lobe, but other lobes are also involved.

patient could not follow commands. Fundoscopic examination showed a salt-and-pepper appearance consistent with retinitis pigmentosa. Serum lactic acid was elevated, but other chemical levels were unremarkable. A muscle biopsy of the thigh showed raggedred fiber appearance, consistent with mitochondrial myopathy.

CT scans without contrast showed prominent basal ganglia calcification and hypodense lesions with atrophy, especially in both parietooccipital regions (Fig. 2A). There was no enhancement with contrast administration. MR images best demonstrated the abnormal brain tissue as high signal on T2-weighted images (Figs. 2B-2D).

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Discussion

The most commonly noted CT findings in these patients are parietal (n = 8) and occipital (n = 7) focal hypodensities, both of which were present in our patient [1, 4–6]. Less commonly involved are the temporal (n = 4) and frontal (n =2) regions. Lesions are usually bilateral, either symmetric or asymmetric. Generalized atrophy was a prominent feature in both our cases and was often mentioned in the description of other cases, with prominent dilatation of the occipital horns. Focal white matter hypodense lesions, especially parietooccipital, have been described in Kearns-Sayre syndrome, but these lesions differ from MELAS in that they occur less frequently (40% of cases), are smaller, and appear to spare the cortex, at least as evidenced on CT [7, 8]. Although cerebellar involvement is characteristic of MERRF syndrome, it has been described pathologically in at least one case of MELAS [6]. Both our patients had cerebellar lesions noted on MR scans, a finding not previously reported. However, in neither patient were these lesions the dominant finding, nor were there focal abnormalities in the brainstem or spinal cord as has been reported pathologically in MERRF [3].

Some authors have emphasized the difficulty of classifying mitochondrial myopathies as well as overlap of syndromes [6, 9]. In one of the largest series (n = 66) of histologically proved disease, CT findings were summarized in 35 patients [9]. Only half showed abnormalities; cerebral atrophy in 18, cerebellar atrophy in 12, hypodense white matter in five, basal ganglia calcification in four, major infarcts in three, and lacunar

infarcts in two. Of these patients, two had strokelike episodes but neither was short nor had lactic acidosis, thereby not meeting all the major criteria for the diagnosis of MELAS syndrome.

Most patients with MELAS syndrome are affected in youth or early adulthood, but the course of lesion appearance has infrequently been studied. One patient with a small frontoparietal hypodensity had resolution of this lesion and appearance of bilateral parietal lesions 3 months later [1]. Another patient had four separate lesions appear over a 6-month period, with resolution of the first two by the time the last two were studied with CT [5]. The lesions in our patients as well as those in at least one other who had sequential scans showed progressive appearance of lesions without resolution of prior ones [1]. Usually, MELAS syndrome has an episodic and progressive chronology, with resolution of focal lesions seeming to occur only with generalized atrophy. Our experience with MR suggests that abnormal prolonged T2 signal persists in areas of insult.

Other than our case 1, we could find no reference to contrast enhancement in the described lesions. Although one could postulate that the gyral enhancement noted in our patient was an indication of the lesion's subacute chronology with blood-brain barrier breakdown, this could not be verified by neurologic examination. Other unexplained findings in the literature include right extracranial carotid occlusion in one patient [1] and questionable slow flow on angiography in our case 2. As MELAS patients have intracranial lesions that do not correlate with strictly vascular territories, the significance of these findings is unknown. Pathologically, the vessels are unaffected in these patients except for being the site of iron-mucopolysaccharide deposition in the basal ganglia [6]. However, the clinical course may be confused with that of a vasculitis, as occurred in both of our cases.

Calcification or hypodense lesions in the basal ganglia are often noted. Two patients in the literature were noted to have low-density areas resembling lacunae [1]. Our case 1 had hypodense lesions in the caudate, internal capsule, and thalamus. Although basal ganglia calcification was noted on CT scans in three patients, pathologic examination showed calcification in another three who did not have CT scans [1]. Our case 2 had calcifications located in the caudate, globus pallidus, and putamen. Similar hypodense or calcified lesions occur in patients with Kearns-Sayre syndrome, which is occasionally associated with hypoparathyroidism or pseudohypoparathyroidism [2, 7, 8].

Although the lesions were not seen on T1-weighted images, they did have high signal on T2-weighted images, as do most CNS diseases [10]. We believe that involvement of the temporal lobes and cerebellar hemispheres in patients with ME-LAS syndrome may be more frequent than reported. Both our patients had prolonged T2-signal lesions in these regions that were not seen on CT scans. Other patients may have had involvement here as well, but the lesions may have been obscured by CT-related bony artifact [10]. Quite impressive was the involvement of the optic radiations and adjacent occipital cortex, easily explaining the dominant clinical finding of blindness. Also, MR clearly shows that the lesions involve both cortex as well as white matter, with relative sparing of the frontal lobes and brainstem. The only drawback of MR is its inability to demonstrate basal ganglia calcification, which may be a prominent feature.

Although the biochemical disorder in mitochondrial myopathies is not known exactly, various enzymatic abnormalities leading to deficient oxidation of nicotinamide adenine dinucleotide have been postulated [3]. Deficient mitochondrial utilization of pyruvate substrates via Krebs cycle results in the serum lactic acidosis noted in these patients. Hayes et al. [4] were able to demonstrate decreased concentrations of phosphocreatine in skeletal muscle and possibly brain in a patient with MELAS syndrome utilizing phosphorus-31 spectroscopy. This finding is nonspecific, however, having been reported in other ischemic tissues such as myocardium [11].

The diagnosis of MELAS syndrome, as well as other mitochondrial myopathies, can be confirmed by muscle biopsy [2]. Light microscopy of muscle prepared with modified Gomori trichrome stain will show a characteristic ragged-red fiber appearance, and electron microscopy will show numerous enlarged mitochondria with globular lipid inclusions [3]. The histology of brain lesions is less well described, but has generally been referred to as a spongy degeneration with coarse vacuolation [2]. The most detailed pathologic description of brain in MELAS noted the following: brain atrophy with enlarged occipital horns, severe loss of neurons, focal gliosis, spongy alteration of layers of the cortex, microcystic liquefaction that produced a uniform outlining of the cortical ribbon, and an iron-mucopolysaccharide-calcium complex deposition in the perivascular regions of the basal ganglia [6]. Although it is clear that there is extensive brain destruction in MELAS syndrome, the exact cause of the lesions is unclear.

In summary, of the mitochondrial myopathies, MELAS syndrome has the most extensive neuroimaging abnormalities, including infarctlike areas bilaterally in the posterior brain almost always and calcification or hypodensities in the basal ganglia region in over half the cases. The radiologic differential diagnosis for this appearance includes multiinfarct dementia, postinflammatory or posttraumatic change, anoxic injury, vasculitis, Cockayne syndrome, Canavan sclerosis, Wilson disease, Leigh disease, Alper disease, Lafora disease, Krabbe disease, Fahr disease, cereoid lipofuscinosis, adrenoleukodystrophy, and progressive multifocal encephalopathy [12]. Correlation of scan findings with the clinical history of strokelike episodes in a short person should lead to the correct diagnosis when serum lactic acid levels are elevated. MR imaging best shows the extent of brain involvement, including both gray and white matter, that might not be seen on CT.

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