A Case of Melas (A3243G) on Chronic Dichloroacetate Treatment

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Dear Sir,

Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is a severe mitochondrial disease for which the currently available therapeutic options are largely supportive and the prognosis remains substantially poor. Interestingly, sodium dichloroacetate (DCA) has been consistently shown to reduce lactic acidemia, present in mitochondrial disorders, by increasing the activity of the pyruvate dehydrogenase complex [1]. Here we describe a MELAS patient treated for almost seven years with DCA. Although further recurrence of headache, abdominal pain and stroke-like episodes was prevented, DCA exacerbated a preexistent peripheral neuropathy.

In 1996, D.F., a 17-year-old male, developed a right temporo-occipital ischemic stroke, characterized by a migraine attack-like onset and left lateral homonymous hemianopsia, followed by generalized seizures. Although the CT scan of the brain evidenced a right temporo-occipital lesion, the neurological deficits recovered completely during the next days. In fact, 6 months later the lesion was not any more documented at the brain MRI scan. Two years later, the patient experienced a migraine attack with visual aura, followed by left hemianopsia and weakness in his left hand. A brain MRI evidenced a wide right ischemic lesion involving both cortical and subcortical matters; the EEG showed a gen-

eralized epileptic dysfunction, more marked in the right regions, and phenytoin was started. Mild perceptive deafness was also present. CSF and plasma routine examination was normal. The EMG suggested a moderate axonal neuropathy, mainly involving the lower limbs. Since the muscular biopsy was compatible with mitochondrial involvement, leukocyte mitochondrial DNA was sequenced, showing an A3243G mutation. In 1999, D.F. experienced gener-

alized seizures, diplopia, blurred vision and left hemianopsia. A ^{99m}Tc-SPECT of the brain evidenced a severe hypoperfusion, especially in the right temporo-occipital area (fig. 1A), and the EEG showed a complex partial seizure pattern. DCA was started at the dose of 2400 mg/day, coupled with vitamin supplementation. Three months later, a SPECT scan showed milder signs of hypoperfusion also in the left side (fig. 1B). Moreover, due to the unsatisfactory control

Fig. 1. Serial ^{99m}Tc-SPECT brain scans. Before starting DCA administration, a severe hypoperfusion in the right temporo-occipital regions was already evident (**A**, Jan. 1999), and, 3 months later (**B**), milder signs of hypoperfusion also appeared in the homologous left areas. About one and half years following DCA introduction, the cerebral perfusion in the left regions had significantly recovered, and this pattern was stable at the follow-up in May 2004 (**C**). The finding is in line with the previous report by Sudo et al. [9], in which the therapeutic effect of DCA in a MELAS patient was paralleled by an improvement of the pattern of cerebral perfusion assessed by [¹²³I]IMP SPECT.

Table 1. Arterial blood lactate determinations

Date	Arterial blood lactate mM	DCA dose mg/day
Jan. 1999	4.99	–
Mar. 1999	3.28	2,400
Apr. 1999	5.62	2,400
Oct. 2000	5.81	1,600
Nov. 2001	5.00	1,600
May 2002	4.50	1,600
May 2004	6.30	1,600

Although the patient received relatively high doses of DCA for a protracted period of time, lactate persisted to be elevated.

over the seizures, phenytoin was changed for barbiturates and, since then, no further epileptic manifestations were reported. In 2000, a brain SPECT scan showed a complete restore of the perfusion in the left regions, while the EMG documented a worsening of the pre-existing neuropathy, now with active signs of denervation. Consequently, DCA was reduced to 1,600 mg/day. Two years later, a neuropsychological assessment evidenced deficits in the linguistic and mnemonic performances, and the polyneuropathy was stable at the EMG, but now without active signs of denervation. At September 2005, the patient was substantially unchanged, although the neuropsychological assessment evidenced a slight worsening. Since DCA was well tolerated the treatment was not interrupted.

Both the response to DCA and the side effects described here appear to be in line

with previous reports [2–5]. Although a mild alteration of the hepatic function was evidenced, no major signs of toxicity were shown, as confirmed in 2005 by the liver ultrasonography. Interestingly, in order to minimize DCA side effects it has been suggested a dose adjustment according to the blood lactate levels [4]. However, although D.F. received relatively high doses of DCA for a protracted period of time, lactate persisted elevated (table 1). Nevertheless, we observed a reduction of the incidence of stroke-like episodes and recurrent headache, without stopping the neuropsychological deterioration. These observations suggest that lactate blood concentrations may not exactly predict the therapeutic activity of DCA or one patient's response to the drug. Moreover, an important peripheral neuropathy, already present before starting DCA, was evidenced. Peripheral neuropathy has already been described both in MELAS and in patients receiving high doses of DCA for long periods of time [5, 7]. In fact, a recent trial in MELAS was interrupted because of the important worsening of new onset or pre-existing peripheral neuropathies [8]. The authors concluded that, because of the early termination, not enough power was reached for determining the potential effectiveness of DCA and that toxicity overshadowed the potential benefits. Although in our patient DCA clearly worsened the neuropathy, the decrease of the dose determined an improvement, and the discontinuation was not accepted. These findings seem to indicate that the therapeutic effect was achieved at a dose for which the polyneuropathy was not furthermore exacerbated, and we would like to conclude suggesting that further investigation may be required in order to optimize the therapeutic window of DCA.

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