MITOCHONDRIAL DISEASES ASSOCIATED WITH CEREBRAL FOLATE DEFICIENCY


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EXTENSION OF THE CLINICAL SPECTRUM OF DANON DISEASE

Danon disease is caused by mutations in the lysosome-associated membrane protein 2 (LAMP2). It is an X-linked dominant disorder characterized by severe cardiomyopathy, mental retardation, and mild myopathy in men, and cardiomyopathy in female carriers. All mutations reported so far have resulted in absence of LAMP2 staining in affected men.

Case reports. The proband, III-4 (figure e-1 on the Neurology® Web site at www.neurology.org), with normal intelligence, was referred at age 46. Since childhood, he had slowly progressive weakness of legs and later arms, with subsequent dysarthria and swallowing difficulties. He is now 63 and is almost completely wheelchair bound. His vision has gradually diminished to finger counting. Examination showed an amyopathic face, gynecomastia, moderate weakness of limb girdle muscles, and minor distal weakness. Perimetry demonstrated central scotomas, while fluorescein angiography showed a Bullseye maculopathy, but electroretinography was normal. At the age of 61 a pacemaker was implanted because of a sick sinus syndrome. Echocardiography revealed left ventricular hypertrophy with preserved systolic function.

Subject III-3 presented at the age of 63 years with muscle weakness since age 45. His intellect and vision were normal. In retrospect, he had been a little weaker than his peers since his teens. He showed predominant distal weakness of the legs. He had symptomatic paroxysmal atrial fibrillation. Echocardiography revealed left ventricular hypertrophy with preserved systolic function.

Subject III-1 has weakness of shoulder and upper arm muscles, with predominant distal weakness of the legs. He has no cardiac abnormalities or mental retardation.

Subject III-2 is asymptomatic at the age of 70 years.

Subject III-5 died at the age of 13 years due to a neurologic disease (spasticity) and mental retardation. No medical data could be obtained.

Subject III-6 had progressive walking disabilities since age 64. He was known to have macular degeneration and unexplained liver function disturbances. On examination, at age 69, he had moderate proximal arm weakness, with slight proximal weakness and more pronounced distal weakness of the legs.

Subject II-1 was said to have had proximal muscle weakness and palpitations; she died suddenly at the age of 61 years.

Subject II-5 was said to have had difficulties in climbing stairs.

Subject IV-9, formerly healthy, died suddenly at the age of 28 years.

Additional studies. In Individuals III-1, 3, 4, and 6 serum CK activity was two to four times the upper limit of normal and muscle biopsy of the latter three showed autophagic vacuoles (figure), with glycogen accumulation. At the ultrastructural level (III-3, 4) lipid droplets, large amounts of lipofuscin, myelin figures, and abnormal (increased) amounts of glycogen were found. Acid maltase in leukocytes was normal. LAMP2 immunohistochemical staining of skeletal muscle showed irregular distribution with increased expression in the vacuolated fibers. On Western blot LAMP2 was not significantly reduced. LAMP2 molecular analysis revealed a new missense mutation c.1150G>C (reference sequence NM_013995.1), in splice variant B (exon 9B), leading to an amino acid change (p.Gly384Arg). This mutation was present in III-1, 3, 4, and 6, and IV-9, but not in III-2 nor in over 100 control alleles. Fundus photographs demonstrated peripheral pigment clumping (III-3) and decreased pigment (III-4) in the macular region.

Autopsy in IV-9 showed a hypertrophic and slightly dilated heart (429 g) with widespread degenerative changes and some vacuoles.

Discussion. In this report, we describe a family with a novel missense mutation in the LAMP2B isoform resulting in a subtype of Danon disease characterized by a much milder cardiac phenotype in men, with progressive, generalized severe
Muscle weakness without mental retardation, and normal LAMP2 protein staining. LAMP2 staining in the skeletal muscle of our patients is probably due to the fact that the missense mutation might still result in a stable LAMP2B protein.

Mental retardation, although common in Danon disease (70% in men), was not observed in our family. This was also the case in a Japanese family in which a 2 bp deletion (truncating) mutation in isoform B was found.

It is notable that the mutation described in our family gave rise to sudden cardiac death in a female carrier (IV-9). The severe progressive myopathy found in our family is not a common feature in Danon disease. Previously described patients have had rather mild proximal muscle weakness. Whether this is due to the fact that most men with Danon disease die because of heart failure before the age of 30 years and are therefore not able to develop more severe myopathy or whether this is related to the specific isoform missense mutation is unclear. Some case reports describe progressive decrease of visual acuity. The recently described fundus abnormalities in Danon disease are remarkably similar to those found in our family.

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5. Nomenclature according to http://www.hgvs.org/mutnomen/


MITOCHONDRIAL DISEASES ASSOCIATED WITH CEREBRAL FOLATE DEFICIENCY

Cerebral folate deficiency (CFD) has been defined as any neuropsychiatric condition associated with isolated lowering of 5-methyltetrahydrofolate (5-MTHF) levels in CSF and normal systemic folate metabolism.

CFD has been detected in the infantile-onset CFD syndrome (mediated by serum folate receptor [FR] autoantibodies of the blocking type) and Aicardi-Goutières and Rett syndromes. In Kearns-Sayre syndrome (KSS), systemic folate deficiency or low CSF 5-MTHF have long been recognized. Because active transport of 5-MTHF across the choroid plexus epithelial cells is mediated by ATP-dependent processes, we conducted a study to determine CSF 5-MTHF in a series of patients with mitochondrial disorders.

Methods. Twenty-eight patients with different mitochondrial disorders and fulfilling the previously defined diagnostic criteria were recruited from the Hospital Sant Joan de Déu, Barcelona, Spain (21 patients), the University Clinic Aachen, Germany (5 patients), and Hospital 12 de Octubre, Madrid, Spain (2 patients). Diagnosis included KSS (5 patients), neuropathy, ataxia, and retinitis pigmentosa (1 patient), mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (1 patient), and various clinically heterogeneous respiratory chain enzyme deficiencies (RCD) (21 patients). Brain MRI was performed for each patient. Serum folate and CSF 5-MTHF, glucose, protein, and cells were determined as per established protocol. CSF 5-MTHF was analyzed by high-pressure liquid chromatography with fluorescence detection. Values for patients were compared to our reference controls (n = 63). Serum samples from five patients (Patients 10–14, table) were tested for FR autoantibodies of the blocking type.

Statistical analysis (Spearman test, SPSS 12.0 program) was applied to determine a possible correlation between CSF folate and protein concentration.

Results. Despite normal serum folate levels, 14 patients (mean age: 9.5 years; range: 3 months–34 years; Patients 1–14, table) had low CSF 5-MTHF concentrations (mean: 22.1 nmol/L; range: 0.6–48.8 nmol/L). The lowest 5-MTHF values were found among four of the five patients with KSS. Ten patients showed white matter demyelination and 12 basal ganglia involvement. Serum tested negative for FR blocking type autoantibodies in five patients (Patients 10–14, table; the remaining patients were not tested). In patients presenting CFD, CSF protein and 5-MTHF concentrations had a strong statistical relation (the highest the protein the lowest the 5-MTHF values; p < 0.001; r = −0.85). However, this association was not significant in patients with CFD and no KSS (p = 0.18, r = −0.52). Fourteen out of 28 patients had serum folate and CSF 5-MTHF values within the normal range (Patients 15–28, table). CSF protein levels were normal and no correlation was observed between CSF protein and 5-MTHF values. MRI white matter abnormalities were detected only in one patient (Patient 16, table).

Discussion. Our results indicate that mitochondrial disorders, and in particular KSS, constitute a new group of patients who are at risk from secondary CFD.

Half of our patients (14 out of 28) had CFD. However, 5 out of these 14 patients had KSS, a mitochondrial DNA deletion giving rise to pigmentary retinopathy, external ophthalmoplegia, ataxia, and aberrant cardiac conduction, which is a well recognized entity associated with low CSF folate levels. We detected very low CSF folate concentrations in KSS, whereas in those with RCD the deficiency was less marked. Autopsy studies in KSS have documented oncocytic transformation of choroid plexus epithelial cells with abundant deletions in mitochondrial DNA and decreased expression of mitochondrial DNA encoded proteins. In this sense, choroid plexus dysfunction may explain both high CSF protein and low 5-MTHF, as well as the strong correlation between the two variables found in this study. Additionally, the uptake of folate by choroid plexus epithelial cells is accomplished by ATP-dependent FR-mediated endocytosis. Reduced folate CSF levels found in our patients with diverse RCD and not clearly related to the CSF protein concentration could be due to failure of this energy dependent folate transfer.

In our series, 10 out of 14 patients with CFD presented white matter MRI demyelination signs, whereas only one patient with normal CSF folate disclosed similar changes. As folate is essential for methylation reactions, myelin basic protein methylation failure, with a consequent instability of myelin, may contribute to these MRI findings.

The good response to folic acid observed in a recently reported patient with KSS and the results of the present work indicate the need to ex-
### Table: Characteristics of patients with cerebral folate deficiency and normal CSF folate levels

<table>
<thead>
<tr>
<th>Age, y/sex</th>
<th>Clinical diagnosis</th>
<th>Brain MRI alterations</th>
<th>Enzymatic abnormalities*</th>
<th>Genetic abnormality</th>
<th>CSF 5-MTHF, nmol/L</th>
<th>CSF proteins,† mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 13/F</td>
<td>NARP</td>
<td>BG, WM, cerebellum (atrophy)</td>
<td>Normal</td>
<td>8993 mutation</td>
<td>39 (low) (N: 45–94)</td>
<td>34</td>
</tr>
<tr>
<td>2 22/M</td>
<td>Kearns-Sayre</td>
<td>BG, WM</td>
<td>Normal</td>
<td>4.977 pb deletion</td>
<td>0.6 (low) (N: 45–94)</td>
<td>244</td>
</tr>
<tr>
<td>3 7/M</td>
<td>Kearns-Sayre</td>
<td>WM, BG, cerebellum (atrophy)</td>
<td>CI-III muscle</td>
<td>4.120 pb deletion</td>
<td>8 (low) (N: 45–94)</td>
<td>89</td>
</tr>
<tr>
<td>4 34/F</td>
<td>Kearns-Sayre</td>
<td>BG, cerebellum (atrophy), WM</td>
<td>Normal</td>
<td>2.434 pb deletion</td>
<td>24 (low) (N: 45–94)</td>
<td>80</td>
</tr>
<tr>
<td>5 11/M</td>
<td>Kearns-Sayre</td>
<td>WM, BG, brainstem (high T2 intensity)</td>
<td>CI-CIII muscle</td>
<td>In course</td>
<td>6 (low) (N: 41-117)</td>
<td>121</td>
</tr>
<tr>
<td>6 17/F</td>
<td>Kearns-Sayre</td>
<td>WM, brain atrophy, brainstem (restricted DQ)</td>
<td>BG</td>
<td>Normal</td>
<td>Multiple deletions</td>
<td>2 (low) (N: 41-117)</td>
</tr>
<tr>
<td>7 1/M</td>
<td>Encephalopathy</td>
<td>BG, WM</td>
<td>CIV muscle, Fb</td>
<td>None</td>
<td>33 (low) (N: 48-127)</td>
<td>31</td>
</tr>
<tr>
<td>8 1/M</td>
<td>Leigh, lactic acidosis</td>
<td>BG</td>
<td>Normal</td>
<td>None</td>
<td>17 (low) (N: 48-127)</td>
<td>30</td>
</tr>
<tr>
<td>9 3 mo/M</td>
<td>Encephalopathy and lactic acidosis</td>
<td>BG, cortical atrophy</td>
<td>CI+ III/III+III, low CoQ10 M and Fb</td>
<td>None</td>
<td>22 (low) (N: 67-195)</td>
<td>305†</td>
</tr>
<tr>
<td>10 1/M</td>
<td>Encephalopathy and lactic acidosis</td>
<td>BG, WM, brainstem demyelination, moderate cortical atrophy</td>
<td>CI muscle</td>
<td>None</td>
<td>38 (low) (N: 64-182)</td>
<td>25</td>
</tr>
<tr>
<td>11 12/F</td>
<td>Leigh</td>
<td>BG, WM, moderate cortical atrophy</td>
<td>CIV muscle</td>
<td>None</td>
<td>23 (low) (N: 41-117)</td>
<td>29</td>
</tr>
<tr>
<td>12 5/M</td>
<td>Encephalopathy and lactic acidosis</td>
<td>BG, WM, cerebellar white matter dysmyelination and atrophy</td>
<td>Mitochondrial depletion suspected</td>
<td>None</td>
<td>24 (low) (N: 41-117)</td>
<td>55</td>
</tr>
<tr>
<td>13 6/M</td>
<td>Encephalopathy</td>
<td>Moderate cortical and cerebellar atrophy</td>
<td>CIII + IV Fb</td>
<td>None</td>
<td>21 (low) (N: 41-117)</td>
<td>46</td>
</tr>
<tr>
<td>14 4/M</td>
<td>Encephalopathy and lactic acidosis</td>
<td>Cortical atrophy</td>
<td>CIII muscle</td>
<td>None</td>
<td>48 (low)</td>
<td>15</td>
</tr>
<tr>
<td>15 13/F</td>
<td>MELAS</td>
<td>Occipital stroke-like image</td>
<td>Normal</td>
<td>8993 Mutation</td>
<td>81 (N: 45-94)</td>
<td>20</td>
</tr>
<tr>
<td>16 3/F</td>
<td>Acute encephalopathy, lactic acidosis</td>
<td>Patchy white matter high intensity images</td>
<td>CI, CII, and CIII, normal CoQ10 muscle</td>
<td>None</td>
<td>70 (N: 63-111)</td>
<td>18</td>
</tr>
<tr>
<td>17 6 mo/F</td>
<td>Encephalopathy, lactic acidosis</td>
<td>Progressive brain and cerebellar atrophy</td>
<td>CI, CII, and CIII, normal CoQ10 muscle</td>
<td>60% mit DNA depletion</td>
<td>82 (N: 48-127)</td>
<td>14</td>
</tr>
<tr>
<td>18 2/M</td>
<td>Encephalopathy and hepatic disease</td>
<td>Progressive brain and cerebellar atrophy</td>
<td>Nonsignificant generalized deficiencies muscle</td>
<td>93% mit DNA depletion</td>
<td>64 (N: 44-122)</td>
<td>23</td>
</tr>
<tr>
<td>19 10 mo/F</td>
<td>Leigh syndrome</td>
<td>BG</td>
<td>CI, CII, CIII, and CIV muscle</td>
<td>None</td>
<td>84 (N: 48-127)</td>
<td>22</td>
</tr>
<tr>
<td>20 1/F</td>
<td>Leigh syndrome</td>
<td>BG</td>
<td>CI, CII, and CIII, normal CoQ10 muscle</td>
<td>None</td>
<td>82 (N: 48-127)</td>
<td>24</td>
</tr>
<tr>
<td>21 1 mo/F</td>
<td>Neonatal encephalopathy, lactic acidosis</td>
<td>BG</td>
<td>Normal</td>
<td>None</td>
<td>101 (N: 48-127)</td>
<td>41</td>
</tr>
<tr>
<td>22 6 mo/M</td>
<td>Encephalopathy, lactic acidosis</td>
<td>Brain atrophy</td>
<td>Generalized deficiencies muscle</td>
<td>None</td>
<td>64 (N: 48-127)</td>
<td>15</td>
</tr>
<tr>
<td>23 8/M</td>
<td>Leigh syndrome, lactic acidosis</td>
<td>BG</td>
<td>Normal</td>
<td>None</td>
<td>72 (N: 45-94)</td>
<td>34</td>
</tr>
<tr>
<td>24 3 mo/M</td>
<td>Encephalopathy, lactic acidosis</td>
<td>BG and brain atrophy</td>
<td>CIV muscle</td>
<td>None</td>
<td>89 (N: 48-127)</td>
<td>18</td>
</tr>
<tr>
<td>25 4 mo/F</td>
<td>Encephalopathy, cardiomyopathy, lactic acidosis</td>
<td>Brain and cerebellum atrophy</td>
<td>CIII, IV, V muscle</td>
<td>44% depletion mit DNA (heart)</td>
<td>87 (N: 48-127)</td>
<td>29</td>
</tr>
<tr>
<td>26 12/M</td>
<td>Encephalopathy and lactic acidosis</td>
<td>Cerebellum atrophy</td>
<td>Normal</td>
<td>None</td>
<td>55 (N: 45-94)</td>
<td>17</td>
</tr>
<tr>
<td>27 5 mo/F</td>
<td>Encephalopathy and lactic acidosis</td>
<td>Brain and cerebellum atrophy</td>
<td>Generalized deficiencies muscle</td>
<td>None</td>
<td>58 (N: 48-127)</td>
<td>25</td>
</tr>
<tr>
<td>28 13/F</td>
<td>Mental retardation, retinitis pigmentosa, hypoacusia, ragged red fibers</td>
<td>Cerebellum atrophy and bilateral pallidum high intensity images</td>
<td>Normal</td>
<td>None</td>
<td>67 (N: 45-94)</td>
<td>26</td>
</tr>
</tbody>
</table>

*Respiratory chain complex deficiencies reported were below 20% of the reference activity values in every case.
†Normal values for protein concentration: 15–40 mg/dL.
‡High value related to hemorrhagic puncture. DQ = diffusion quotient.
NARP = neuropathy, ataxia, retinitis pigmentosa; BG = basal ganglia; WM = white matter; N = normal values of our control population; Fb = fibroblasts; MELAS = mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke.
tend the CSF 5-MTHF analysis, maybe as a routine measurement, in order to have larger series and to establish the real prevalence of CFD in mitochondrial disorders. Moreover, high dose of folic acid supplementation (from 1 to 3 mg/kg/day) to correct low CSF 5-MTHF may be recommended in these disorders.

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David W. Dodick, MD

EXTRACEPHALIC CLUSTER (CLUSTER SINE HEADACHE)

A 67-year-old woman presented to the emergency department with left sided chest tightness and left arm pain with paresthesia.

Over the past 6 years, she had a circannual pattern of stereotyped attacks occurring predictably during the winter solstice, lasting approximately 6 weeks. The majority of attacks would abruptly awaken her from sleep, with excruciating left sided chest, jaw, arm, back, torso, and abdominal pain. Each episode lasted 1 to 2 hours untreated and was accompanied by paresthesias that would begin over the left side of her chest and march over 10 minutes to involve her left face, then arm and hand, and finally her medial left thigh. During each of the one to three daily episodes, the patient experienced restlessness and felt the need to pace. On previous emergency visits, the patient made the observation that 100% oxygen provided symptomatic relief faster than the untreated duration of her attacks. There was no history of headache, cranial autonomic symptoms or signs, nausea, photophobia, or phonophobia associated with these episodes. She does not drink alcohol and is unaware whether nitroglycerin triggers her attack. The patient had no personal or family history of migraine, cluster headache, or visual aura.

She had extensive cardiology evaluations including angiography, exercise echocardiograms, and electrocardiograms, all of which were normal. In particular, she had a 24-hour telemetry during and between her attacks without any electrocardiographic differences.

On examination, vital signs and results of general physical and neurologic examinations were normal. Complete blood count, serum chemistry, urinalysis, and head and neck MRI/MRA had normal results.

The patient was treated with verapamil 80 mg three times daily at the beginning of her cluster cycle. Within 4 days, her attacks resolved and have not recurred over the past 6 months.

Discussion. We believe this patient has cluster sine headache with associated sensory aura. The circannual and circadian periodicity, strict unilaterality, nocturnal preponderance of attacks, attack duration, cluster and remission periods, motor agitation during attacks, and response to
oxygen and verapamil support this assertion. Indeed, the patient meets all International Classification of Headache Disorders–II criteria for cluster headache except for location of pain.

A number of unique clinical features warrant comment. First, the most unusual feature is the presence of somatic pain in the absence of headache. In a prospective clinical study of 230 patients with cluster headache, in addition to head pain, pain was also experienced by some patients in extracephalic locations such as the neck and shoulder.1

The potential mechanisms by which extracephalic pain may occur as a manifestation of cluster headache is unclear but reciprocal connections between somatotopically organized hypothalamic nuclear regions, periaqueductal gray, and the trigeminal-cervical complex likely account for pain referral in occipital and extracephalic regions in patients with cluster headache.2,3

The presence of sensory aura in this patient would not be considered to be unusual since aura has now been described in patients with cluster headache with a prevalence of 14%.1 Although an EEG was not performed during an attack, the length and periodicity of the attacks and the response to verapamil argue against this being a seizure.

While it could be argued that the swift but open-label response to verapamil is inadequate proof of a therapeutic response, the clinical features of this case are overwhelmingly consistent with the cluster headache syndrome regardless.

Clinicians should be alert to the possibility of atypical, extracephalic locations of pain in primary headache disorders. While these presentations are unique and likely rare, they are probably under-recognized. In this particular case, the patient only came to the attention of a neurologist 6 years after the onset of symptoms, because of the hemisensory symptoms which prompted a stroke consultation. The absence of headache also provides yet one more piece of evidence that cluster headache is a CNS disorder, not simply a neurovascular headache syndrome.

From Mayo Clinic Arizona, Scottsdale.
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