Kearns-Sayre Syndrome with Reduced Plasma and Cerebrospinal Fluid Folate

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A young woman with Kearns-Sayre syndrome and progressive central nervous system deterioration over 15 years had decreased plasma and cerebrospinal fluid folate levels while receiving phenytoin for a seizure disorder. A muscle biopsy showed a "ragged red fiber" myopathy with reduced muscle carnitine and mitochondrial enzymes. Computed tomographic brain scans showed cerebral white matter hypodensities and bilateral calcification of the basal ganglia. The mechanism for the folate deficiency and altered ratio of plasma to cerebrospinal fluid folate is unknown, but the deficiency may be responsive to replacement therapy.


Kearns-Sayre syndrome (KSS) is a multisystem disorder occurring in childhood. It is characterized by the triad of progressive external ophthalmoparesis, conduction heart block, and atypical pigmentary degeneration of the retina, and can be distinguished from other forms of "ophthalmoplegia plus" [2, 11, 16]. An accompanying encephalopathy originally observed postmortem may now be identified in computed tomographic (CT) brain scans as calcification of the basal ganglia or white matter hypodensities [8, 21, 26]. Muscle biopsies show ragged red fibers suggesting a mitochondrial disorder [3]. Endocrinopathies, particularly hypoparathyroidism, have also been observed in some patients with KSS [15]. The neurological symptoms of KSS resemble the syndrome of folate malabsorption [17]. We describe a patient with KSS who was found to have reduced plasma and cerebrospinal fluid (CSF) folate levels without evidence of malabsorption. The patient improved after receiving oral folates, D, L-carnitine, and methionine [9].

Case Report

K.A. was born at 32 weeks' gestation and weighed 2.1 kg. Following six weeks of incubator care, her growth and development were normal until age 9, when generalized absence and tonic-clonic seizures appeared and were treated with phenytoin and phenobarbital. Over the next 11 years, her schoolwork, memory, behavior, coordination, strength, and gait deteriorated. External ophthalmoparesis with bilateral pigmentary degeneration of the retina and bilateral ptosis was first observed at age 12, as was proximal muscle weakness. A serum calcium of 5.0 mEq/L and an Ellsworth-Howard test suggested primary hypoparathyroidism. Thyroid and adrenal function tests were normal but a glucose tolerance test suggested mild chemical diabetes. Electroencephalograms were diffusely slow with frequent, generalized, high-voltage 2 to 3 cps spike-wave discharges. The CSF showed 27 mononuclear cells per milliliter and a protein of 174 mg/dl. CSF glucose, cultures, and the colloidal gold curve were normal. Intravenous injection of edrophonium chloride (Tensilon) produced no effect. The patient was subsequently treated with phenytoin, phenobarbital, acetazolamide, vitamin D (10,000 units), and an antacid (Amphojel).

At age 17, the patient's electrocardiogram showed left axis deviation of $-20^\circ$. IQ was 68 on the Wechsler Adult Intelligence Scale. The first muscle biopsy showed ragged red fibers, but serum creatine kinase levels were normal. Bilateral basal ganglion calcifications and white matter hypodensities were observed in CT brain scan. At age 21 the patient had an episode of unexplained coma. Physical examination was otherwise unchanged. All serum chemical analyses were normal except potassium (2.2 mEq/L), calcium (13.2 mg/dl), and amylase of 385 units, which had decreased to 120 units upon discharge from the hospital. The hematocrit was 24% and the bone marrow was hypocellular but without megaloblastic changes. Serum cobalamin (vitamin B12) and iron levels were normal. Serum calcium had decreased to 7.6 mg/dl at discharge. The patient recovered after several days of hydration and antibiotics. Phenobarbital was discontinued and phenytoin and vitamin D therapy maintained.

By 23 years of age the patient was bedridden and decreased plasma and CSF folate levels were found (Table 1) [23]. Folinic acid was discontinued. A second muscle biopsy showed a low free carnitine (Table 2); esterified carnitine fractions were also similarly decreased although the plasma carnitine was normal (57 and 38 nmol/ml; mean of 59 controls ± standard deviation, 51.07 ± 11.09; range, 35.0–69.8). The urine nitroprusside test (Brand Test) for sulfur-containing amino acids was negative. Treatment was initiated with folic acid, D, L-carnitine, and methionine. A third, post-treatment needle biopsy indicated a slight increase in free carnitine from 2.7 nmol/mg noncollagen protein to 6.94 nmol/mg. During the following year the patient began to walk with the aid of a walker. When she was 25 years of age, a persistent cardiac conduction defect necessitated pacemaker implantation.
Table 1. Plasma and CSF Folate Levels in Patient at Age 23 and in Control Subjects

<table>
<thead>
<tr>
<th>Sample</th>
<th>Plasma Folate (ng/ml)</th>
<th>CSF Folate (ng/ml)</th>
<th>Plasma/CSF Folate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/17/80</td>
<td>1.9</td>
<td>1.1</td>
<td>1.7</td>
</tr>
<tr>
<td>4/7/80</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Posttreatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/25/80</td>
<td>28.0</td>
<td>11.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Control Subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.5–12.9</td>
<td>3–4 times plasma folate levels</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td></td>
<td>8.24 ± 0.43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values are expressed as range from 20 normal control subjects [23].

Methods and Results

Written informed consent was obtained for folate studies when the patient was age 23. During hospitalization hemoglobin, hematocrit, mean corpuscular volume, and serum cobalamin levels were normal. Five, 10-methylenetetrahydrofolate reductase (5,10-MTHFR) activity was normal in leukocytes (study performed by Dr P. Wong, Rush Presbyterian-St. Lukes Hospital, Chicago [31]). A 24-hour urine formiminoglutamate excretion following oral administration of 100 mg/kg of histidine was normal (10.8 mg) [14]. Plasma amino acids were normal with methionine ranging from 11.4 to 57.8 μmol/L (normal range, 6–39 μmol/L) and a CSF methionine of 2.8 μmol/L (normal range, 2.6–3.0 μmol/L) [25]. Folate tissue stores were saturated with 5 mg per day of folic acid intramuscularly for three days before the oral folate absorption study. Then, following an oral dose of 40 μg of folic acid per kilogram of body weight (a total of 1.45 mg, as folvite), folate levels increased to normal; from fasting the values at 30, 60, 90, and 120 minutes were 37, 74, 70, 59, and 47 ng/ml, respectively [6]. The fasting CSF folate was 17 ng/ml with a persistently increased ratio of plasma to CSF folate of 2.2. Pretreatment plasma and CSF folate levels were low, and although plasma levels appeared to respond to oral folate treatment the ratio of plasma to CSF folate remained high (see Table 1). Replacement therapy included 15 mg per day of folic acid, 500 mg per day of methionine, and 10 g per day of D, L-carnitine. The carnitine was reduced to 2 g per day when gastrointestinal intolerance appeared. Supplemental oral leucovorin (6 mg per day) was given for the first two months in addition to folic acid.

Discussion

Abnormally low folate levels have been observed in senile dementias, convulsive disorders, neuropathies, and hypotonia in infants, conditions often without specific causes [20, 22, 27]. Classical homocystinuria (cystathionine synthase deficiency) may also be accompanied by reduced plasma folate [5]. Homocystinuria due to deficient 5,10-MTHFase has recently been associated with a reversed ratio of CSF to plasma folate and reduced muscle carnitine, as well as clinical evidence of a leukoencephalopathy and lipid storage myopathy [1]. Congenital folate malabsorption, a syndrome associated with ataxia, hypotonia, and mental retardation, is also accompanied by megaloblastosis, which was not found in this patient. Undernutrition and phenytoin therapy (which can also cause ophthalmoparesis) reportedly reduce plasma and CSF folates [18, 19, 29]. Severe neurological disability resulting primarily from low folates alone, however, is a disputed occurrence [20].

This patient had all the features of KSS, along with decreased muscle carnitine and mitochondrial enzymes. Studies excluded folate malabsorption and inborn errors of folate metabolism [12]. Although malnutrition and even phenytoin may have some effect on plasma folate, a defect in the distribution of folates is evident in this patient by the persistently low CSF folate levels. Folate deficiency has been associated with altered CSF amine metabolites and neuropsychiatric disorders, but the precise cause of the encephalopathy

Table 2. Mitochondrial Enzymes and Carnitine Concentration in Muscle of Patient at Age 23 and in Control Subjects

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Patient</th>
<th>Control Subjects*</th>
<th>Patient Compared to Control Subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytochrome C oxidaseb</td>
<td>0.27</td>
<td>2.38 ± 0.44 (22)</td>
<td>11.3</td>
</tr>
<tr>
<td>Succinate cytochrome C reductaseb</td>
<td>0.054</td>
<td>1.16 ± 0.47 (17)</td>
<td>4.65</td>
</tr>
<tr>
<td>Citrate syntheteb</td>
<td>1.25</td>
<td>7.88 ± 2.52 (12)</td>
<td>15.9</td>
</tr>
<tr>
<td>Carnitine acetyltransferaseb</td>
<td>1.45</td>
<td>1.57 ± 0.48 (21)</td>
<td>92.3</td>
</tr>
<tr>
<td>Carnitine palmitoyltransferasec</td>
<td>0.60</td>
<td>7.45 ± 1.44 (58)</td>
<td>8.05</td>
</tr>
<tr>
<td>Free carnitine</td>
<td>2.70</td>
<td>19.33 ± 4.77 (68)</td>
<td>13.9</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± standard deviation.

Numbers in parentheses indicate number of control subjects.

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in KSS is unknown [4]. There was a prompt plasma folate response in this patient but the CSF folate was not significantly affected by treatment and the ratio of plasma to CSF folate did not approach normal [13]. Theoretical possibilities include an altered energy-dependent transport system or the excessive binding of folates by proteins in the choroid plexus. A specific primary defect was not apparent in this patient, however [7, 28, 30]. Three other patients in our clinic with calcification of the basal ganglia without the clinical triad of KSS had normal plasma and CSF folate levels (unpublished data, 1982).

The decreased activity of several mitochondria enzymes in the muscle biopsy of this patient is probably the nonspecific consequence of an unknown alteration of the mitochondria [24]. Low carnitine palmitoyltransferase activity has not previously been reported as a secondary phenomenon. One may speculate that there is a basic disorder of mitochondrial enzyme function of unknown cause in KSS which may be influenced by pharmacological amounts of pterins such as folic acid, as well as the related substrates methionine and carnitine [10]. Because a specific mechanism for the increased ratio of plasma to CSF folate in KSS is unknown, however, this abnormality may be an epiphenomenon with an associated nonspecific therapeutic response. Clinical improvement was evident, and there was an increase in muscle free carnitine, although this change may not be important. Additional studies are necessary in patients with KSS, to determine the frequency of abnormalities in the ratio of CSF to plasma folate and to identify a possible pathogenic mechanism.

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References


Case Report: Allen et al: Folate in Kearns-Sayre Syndrome
Xeroderma pigmentosum (XP) is an autosomal recessive disease characterized by accelerated actinic damage to skin and other sun-exposed tissues [15]. Some patients with XP also have a primary neuronal degeneration [15]. The major neurological features of XP include microcephaly, progressive mental deterioration, choreoathetosis, ataxia, sensorineural deafness, areflexia, extensor plantar responses, spasticity, and a neuropathic electromyograph and muscle biopsy [15]. Loss of neurons is prominent in the pyramidal cells of the cortex, the Purkinje cells of the cerebellum, the deep nuclei of the basal ganglia and cerebellum, the zona compacta of the substantia nigra, and the locus ceruleus [15, 17]. In advanced cases the spinal cord pathology resembles that observed in cases of Friedreich ataxia [17]. The constellation of most of these findings with retarded growth and sexual development has been referred to as the De Sanctis–Cacchione syndrome [5, 15].

Cells from patients with XP show abnormal repair of DNA when damaged by ultraviolet (UV) radiation or certain UV-mimetic chemicals [6, 15]. There are currently eight known genetic forms of XP: the variant form, which has abnormal postreplication repair but a normal rate of UV-induced unscheduled DNA repair.