Case Report

Adrenomyeloneuropathy

S Misra*, R Ramesh**, Ch Sita Ramu**, G Srirangalaxmi***, H Radhakrishna****, Vajreswari*****

Abstract

A 29 year old male patient presented with progressive spastic paraparesis of three years duration. He also had gait ataxia which led to recurrent falls. In addition, there was pigmentation of the skin creases, tongue and buccal mucosa. His clinical course was remarkable by recurrent episodes of diarrhea, pulmonary tuberculosis. The investigatory work up showed a normal MRI scan of the brain, spinal cord and normal abdominal structures. The basal serum cortisol levels were low. Adrenomyeloneuropathy was diagnosed and he was started on corticosteroid supplementation. Mineralocorticoid supplementation also is planned in the follow up. The case is being presented for its rarity.

Introduction

Adrenoleukodystrophy was first described in 1923 by Siemörling and Creutzfeldt and the spinal form ‘adrenomyeloneuropathy (AMN)’ was first described in 1976 by Budka et al and later in 1978 by Griffin et al independently. The disease generally starts in the third decade and progresses very slowly and is punctuated by diarrhea and other intercurrent infections.

Progressive spastic paraparesis is often a puzzling entity in clinical medicine. When the imaging does not show a mass lesion or a demonstrable spinal disease such as myelitis, and there is no significant family history, the clinician is at a loss to know what the cause is and how to manage the case. There are many possible considerations that go through the list of differential diagnostic conditions. AMN is rarely given a thought, although it finds its place in the list of conditions in a standard text book.

Case Report

A 29 yr old male patient presented with black discoloration of both hands since the age of 7 yrs and progressive spastic paraparesis since 3 years before admission. He also had several wash-basin attacks in the past 4 months. The gait was ataxic leading to recurrent falls. There was history of recurrent diarrhoeas. He was diagnosed to be having pulmonary tuberculosis 6 months ago and was on antitubercular treatment since then.

There was no history suggestive of any congenital anomalies, retroviral disease, trauma, malabsorption syndrome during his earlier life.

On examination, a thin built male patient with no clinical evidence of malnutrition was having dark pigmentation of the palmar creases and also over the knuckles. There was pigmentation of the buccal mucosa, palate and tongue (Figure 1). His blood pressure was low, 90/60 mm Hg with pulse rate of 100/min. Examination of the cardiovascular, respiratory systems and the abdomen was unremarkable. He was unmarried and there was no testicular atrophy clinically. The nervous system examination showed spastic paraparesis of grade 4/5 power with normal higher intellectual functions, speech, cranial nerves and upper limbs. The ankle reflexes were absent whereas the knee jerks were brisk. There was impairment of joint-position sense and vibration sense at the toes and ankles. There was no sensory loss over the trunk. Romberg’s sign was positive. The gait was spastic-ataxic with swaying towards either side. He did not require any support for walking on even surface.

Investigatory work up showed Hb-11.2 Gm%, TLC-11,400/mm³, Na⁺-129 mEq/ L, K⁺- 4.2mEq/ L, normal chest X-ray, normal ultrasonogram of the abdomen. The cranial computed tomographic study was normal. Abdominal computed tomography for adrenal morphology was also normal. Magnetic resonance imaging study of the brain, cervical and dorsal spinal cord was performed which were normal. Basal serum cortisol levels were low -1.88 micrograms/ dl (normal = 5-25 mcg/ dl). The nerve conduction study suggested axonal sensory motor neuropathy as evidenced by absent sural sensory nerve action potentials (SNAPs) (Figure 2), and mildly reduced amplitudes and velocities of posterior tibial and common peroneal nerves. Cerebrospinal fluid analysis did not show any abnormality.

Analysis of the serum fatty acid composition showed significantly elevated levels of very long chain fatty acids (VLCFA) C:26:0 and C 30:0. There were also higher ratios of C 24:0 / C 22:0 and C 30:0 / C 26:0 (Tables 1 and 2).

He was started on oral prednisolone 40 mg/ day. The dose was gradually reduced to a maintenance dose of 10 mg/ day. The patient is being followed up regularly in the outpatient department and is doing well eleven months after discharge. During this period he discontinued steroids for about ten days during which had a bout of diarrhea and needed intravenous fluid administration.

Discussion

AMN is a variant of adrenoleukodystrophy (ALD). Both the conditions are rare sex-linked disorders transmitted on the X chromosome mapped to Xq28 region. There is a mutation in adenosine 5'-triphosphate binding cassette transporter [ABCD1] gene which codes for a membrane protein of the peroxisomes1. Generally these cases are only anecdotal reports in the literature.2 There was a case report from India, in which AMN was identified nearly 10 years after initial clinical presentation as
paraparesis, when another relative of the index case presented with ALD. Both AMN and ALD are conditions characterized by progressive neurological symptoms and dysfunction of the adrenal glands. Both disorders can cause adrenal insufficiency and hypogonadism in addition to neurological symptoms.

Occasionally, the disease may manifest as Addison’s disease only [in 10% of cases]. In general, ALD tends to present at an earlier age and primarily involves the brain, whereas AMN occurs later and involves the spinal cord. An adult form of ALD is also described with predominant involvement of the brain.

Pathophysiology

Peroxisomal fatty acid β-oxidation pathway has several steps that are catalyzed by different enzymes. The first enzyme in the pathway is fatty acyl-CoA synthetase [Lignoceroyl-CoA ligase], which is defective in X-linked ALD and AMN disorders (Figure 3). As a result, inclusions rich in cholesterol esters with striking excess of saturated unbranched fatty acids of 24 - 30 carbon chain length, of which C:26 and C:25 are most abundant, accumulate in the red blood corpuscles, fibroblasts and other tissues leading to clinical manifestations.

Table 1: Fatty acid composition of the patient and lab controls

<table>
<thead>
<tr>
<th>Fatty Acids</th>
<th>Mohd. Ibrahim</th>
<th>Normal Values GNO</th>
<th>Normal Values CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>C22:0</td>
<td>0.9</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>C24:0</td>
<td>3.0</td>
<td>3.1</td>
<td>2.8</td>
</tr>
<tr>
<td>C26:0</td>
<td>0.36</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C30:0</td>
<td>0.32</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C24:0/C22:0</td>
<td>3.3</td>
<td>3.1</td>
<td>2.8</td>
</tr>
<tr>
<td>C30:0/C26:0</td>
<td>0.9</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

EM = Erythrocyte membrane Phospholipid / Fatty acid composition; GNO = Ground nut oil consumers; CO = Coconut oil consumers; VLCFA = Very Long Chain Fatty Acids with carbon length 22 and above (Long chain fatty acids are those with carbon length 16-20)

‘Body Composition Analysis’ is useful to assess the nutritional status; C 24:0 / C22:0 and C30:0 / C26:0 ratios is useful in knowing the metabolism of VLCFA

Table 2: Fatty acid composition ratio in the patient

<table>
<thead>
<tr>
<th>Erythrocyte membrane Phospholipids Fatty acids composition ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Unsaturates : Saturates</td>
</tr>
<tr>
<td>Oleic Acid : Stearic Acid</td>
</tr>
<tr>
<td>24:0 / 22:0</td>
</tr>
<tr>
<td>26:0 / 24:0</td>
</tr>
<tr>
<td>30:0 / 26:0</td>
</tr>
</tbody>
</table>

AMN is a peroxisomal disorder. Peroxisomes are intracellular organelles responsible for β-oxidation of very long chain fatty acids [VLCFA] – hexacosanoic acid[C26:0], pentacosanoic acid[C25:0] and tetracosanoic acid[C24:0]. These acids get deposited in tissues such as adrenal, gonads, central or peripheral myelin and are responsible for the clinical features.

There is a high variability in the phenotypic expression of ALD/AMN. Nearly 60% of ALD/AMN patients have adenocortical insufficiency. Testicular Leydig cell dysfunction was investigated in AMN/ALD patients by Brennemann et al and 53% of AMN patients had sexual dysfunction in their series. They suggested a name ‘adreno-testiculo-myelo-neuropathy’ instead of AMN. It is also said that serum testosterone/leutinizing hormone [LH] ratio is a more sensitive marker when compared to serum level of either testosterone or LH alone, as evidence of Leydig cell function.

Cerebral involvement occurs in up to a half of AMN sufferers to a variable degree. Both dysmyelination and demyelination can occur in the subcortical white matter. The demyelination is caused by immune mediated perivascular inflammatory reaction in the cerebral white matter. There are also anecdotal reports of psychiatric disturbances in AMN.

The diagnosis of ALD and AMN is established by measurement of absolute levels of C26:0 as well as calculation of the C24:0/C22:0 and C26:0/C22:0 ratios. Infrequently, affected males may have normal levels of C26:0, but all have abnormal ratios. There is no correlation between the absolute VLCFA values and the degree of adrenal, gonadal or neurological involvement. The adrenal insufficiency may either antedate or follow the neurological symptoms. Measurement of cortisol and ACTH levels, ACTH stimulation test, and measurement of testosterone and gonadotropin levels may help in establishing the diagnosis of adrenal insufficiency and primary hypogonadism, respectively. In some cases, an MRI of the brain may show evidence of active demyelination as evidenced by contrast enhancing zones.
Catabolism of VLCFA in peroxisomes

Abnormalities in brain stem auditory-evoked potentials, somatosensory-evoked potentials, visual-evoked potentials and motor and sensory nerve conduction velocities may be found. However, there was a suggestion that treatment with Lorenzo’s oil may be helpful in delaying or preventing the onset of neurological symptoms in asymptomatic but genetically predisposed individuals. The main side effect associated with GTE therapy is thrombocytopenia, which occurs in up to 40% of patients. In the present case, scientists at National Institute of Nutrition, Hyderabad had prepared an edible oil on the lines of Lorenzo’s oil and gave it to the patient for cooking purpose for a period of one year, and wanted to see the change in the fatty acid composition thereafter.

Bone marrow transplantation (BMT) is one of the modalities of treatment offered to these patients. It is not advisable in advanced neurological disease as the neurological deficit might worsen immediately following BMT. In mildly affected cases the results of BMT are encouraging.

**Conclusion**

AMN is an uncommon disease and high index of clinical suspicion is necessary to identify the disease. The need for supplemental steroid introduction warrants an early diagnosis. With the evidence that treatment with Lorenzo’s oil or bone marrow transplantation, or both, may delay the progression of neurological dysfunction in patients with adrenal insufficiency and minimal neurological symptoms and also in genetically predisposed family members, early screening and appropriate referral of these individuals to higher centre, assumes an even more important role.

**Acknowledgement**

I gratefully acknowledge the help provided by Dr. Vajreswari of National Institute of Nutrition in analyzing the samples for the fatty acid composition. I also thank the Endocrinology Department of our Institution for helping in the management of the case.

**References**