Mutant ApoA-1 Amyloidosis in a Family of Five Siblings With Motor Neuron Disease and Dementia

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Abstract

We present a family of five siblings in which three brothers died of motor neuron disease (MND) and in two of them concomitant with dementia. A fourth brother died of myocardial infarction and was found to have extensive aortic intimal apolipoprotein A-1 (ApoA-1) derived amyloid deposits and apoA-1 mutation. Hereditary MND, sometimes associated with dementia, is rare but well documented. ApoE has recently been associated with the MND, Parkinson and dementia-complex. To our knowledge, no family has been reported with concomitant mutant apoA-1 amyloidosis, MND and/or dementia. These findings may suggest an inherited biochemical defect that permits the clinical expression of MND, dementia, atherosclerosis and amyloidosis, or combinations of the three disorders.

Keywords: Amyloidosis; Apolipoprotein A-1; Motor neuron disease; Dementia; Atherosclerosis

Introduction

Apolipoprotein A-1 (ApoA-1) is a high density lipoprotein (HDL) and has a key function in cholesterol transportation. ApoA-1 mutations may lead to inability to synthesise ApoA-1 resulting in HDL deficiency and premature coronary artery disease [1, 2]. ApoA-1 polymorphism has also been described as a risk for early onset non familiar Alzheimer’s disease (AD) [3].

The incidence of familiar adult motor neuron disease (MND) is estimated to be 5% [4] and dementia co-occurring with MND to be 7-14% [4, 5]. Apolipoprotein E has been found in Guamanian MND and Parkinson-dementia complex patients [6] and an association between the apolipoprotein E epsilon 4 alleles and bulbar-onset MND has been described [7]. A case report of a patient with localised amyloidosis with peripheral neuropathy and signs of MND has been presented [8]. To our knowledge, no family has been described with concomitant localised amyloidosis with ApoA-1 mutation, MND and dementia.

Case Report

Clinical, neurophysiological and neuroradiological characteristics of the patients are shown in Table 1. We described a family of five siblings (four brothers and one sister) where three brothers died of a motor neuron disease (MND) and two of them with concomitant dementia. The fourth brother died of coronary infarction and was found to have aortic intimal ApoA-1 derived amyloid deposits associated with an ApoA-1 mutation [9]. He also had memory deficits and computed tomography (CT) of the brain, showed cortical atrophy and slight widening of the ventricles.

Three brothers developed classical symptoms of MND, and two of them were monozygotic twins (G.L. and R.L.). Neurophysiological investigation revealed widespread denervation and low motor nerve amplitudes in all patients. Sensory nerve conduction velocities and amplitudes were normal and motor nerve conduction velocities were only mildly affected in one patient (G.L.). They all died within 2 years. Two of the brothers with MND (H.L. and G.L.) were admitted because of muscle weakness but also of concomitant symptoms of dementia. H.L. was unable to continue work as a repair man in a printing house and G.L. could no...
<table>
<thead>
<tr>
<th>Patient</th>
<th>Men/Women</th>
<th>Born/died (year)</th>
<th>Clinical symptoms of MND</th>
<th>Duration of MND (months)</th>
<th>Clinical symptoms of dementia</th>
<th>EENG/EMG</th>
<th>Computed tomography of the brain</th>
<th>Cardiovascular events</th>
</tr>
</thead>
<tbody>
<tr>
<td>GL</td>
<td>M</td>
<td>1923/1993</td>
<td>Fasciculations, atrophy, increased reflexes and positive Babinski sign</td>
<td>24</td>
<td>Difficulties in ADL, poor memory</td>
<td>Widespread denervation, low motor amplitudes</td>
<td>Cortical and central atrophy</td>
<td>Abdominal aortic aneurysm</td>
</tr>
<tr>
<td>RL</td>
<td>M</td>
<td>1923/1983</td>
<td>Fasciculations, atrophy, decreased reflexes and absent Babinski sign.</td>
<td>20</td>
<td>No</td>
<td>Widespread denervation, low motor amplitudes</td>
<td>Normal</td>
<td>-</td>
</tr>
<tr>
<td>SL</td>
<td>M</td>
<td>1926/1994</td>
<td>No</td>
<td>-</td>
<td>Poor memory, concentration difficulties</td>
<td>ND</td>
<td>Cortical atrophy, Pons infarction</td>
<td>Operated abdominal aortic aneurysm. Died in myocardial infarction 1994</td>
</tr>
</tbody>
</table>

MND: Motor neuron disease; EENG: Electroneurography; EMG: Electromyography; ADL: Activity of daily living; ND: Not done.
longer find his way to the next door supermarket. The fourth brother (S.L.) developed slight dysphasia, decreased memory for recent events and concentration difficulties after a coronary angiography in 1986. CT scan of the brain showed a small infarction on the left side in capsule interna and on the right side in the pons, but also central atrophy and slight widening of the ventricles. The memory problems persisted. This patient died of myocardial infarction in 1994. Pathological examination revealed extensive intimal ApoA-1 derived amyloid deposits and associated with ApoA-1 mutation. The only sister (U.G.) had rheumatic fever as a child and got an artificial mitral valve prosthesis in 1977. She was treated with warfarin. In 1995 she suffered a cerebral infarction with slight right-sided weakness and difficulties in reading and writing. No symptoms of MND or dementia developed before she died of heart congestion and cardiac arrest in 1997.

**Discussion**

Our three family cases of MND represent a hereditary form which may account for at least 10% of MND cases [10]. One pair of identical twins in our report is compatible with either a dominant or recessive inheritance of the disease. In two of our cases with MND and in one further brother without clinical signs of MND, dementia was a prominent feature. Dementia and Parkinsonism is often occurring in the Guam and Mariana Islands form of MND [11]. Also the occurrence of family MND and frontotemporal dementia is well known [12]. This suggests that the pathological findings in family MND may not be restricted to upper and lower motor neurons.

ApoE amyloid deposits in Guamanian MND and Parkinson-dementia patients have been reported [6]. The relationship between ApoE and MND is uncertain with reports of no association [13] and reports of ApoE as a possible contributing factor and depending on age [14]. The relationship between Alzheimer dementia and ApoE amyloid deposits is, however, well established [15]. Systemic amyloidosis is often associated with peripheral neuropathy with prominent autonomic disturbance. In one case report a patient with primary amyloidosis and peripheral neuropathy and signs of MND was described [8]. Our family is interesting, because one of the patients was found to have ApoA-1 derived amyloid deposits in intimal aorta and in association with atherosclerotic plaques. Wild type ApoA-1 derived amyloid in atherosclerotic plaques of the aorta is common and can be found in about 20-30% of autopsy cases [16]. The mutation of the ApoA-1 gene in this case, might reinforce the amyloidogenic properties of the protein. Since amyloid fibrils have been shown to be toxic to cells, ApoA-1 derived amyloid may contribute to the atherosclerotic process, together with cholesterol. The severe atherosclerotic lesions might be a consequence of the ApoA-1 mutation, which results in both HDL deficiency and extensive amyloidosis. Unfortunately the patients with MND could not be evaluated for amyloid except a muscle biopsy from G.L. which was negative for amyloid. The co-occurrence of heart congestion and claudication may theoretically suggest that these patients could have the ApoA-1 mutation. Our findings may suggest an inherited biochemical defect that permits the clinical expression of MND, dementia or amyloidosis with atherosclerosis, or combinations of the three disorders.

**References**

11. Hudson AJ. Amyotrophic lateral sclerosis and its association with dementia, parkinsonism and other


