Elmer Press

Case Report

J Neurol Res • 2011;1(4):161-164

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

Magnus Vrethem[a, b, e], Gerd Mucchiano[c, d]

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

Manuscript accepted for publication October 17, 2011

[a]Neurology, Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linkoping University, Department of Neurology and Neurophysiology, County Council of Ostergotland, Linkoping, Sweden
[b]Clinical Neurophysiology, Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linkoping University, Department of Neurology and Neurophysiology, County Council of Ostergotland, Linkoping, Sweden
[c]Department of Pathology, Linkoping University, Linkoping, Sweden
[d]Borne-og ungdomspsykiatrisk Center, Bispebjerg Hospital, Kopenhamn, Denmark
[e]Corresponding author: Magnus Vrethem, Email: magnus.vrethem@lio.se

doi:10.4021/jnr63w

Table 1. Clinical, neurophysiological and neuroradiological findings in a family with amyloidosis, MND and/or dementia

Patient	Men/ Women	Born/died (year)	Clinical symptoms of MND	Duration of MND (months)	Clinical symptoms of dementia	EENG/EMG	Computed tomography of the brain	Cardiovascular events
HL	M	1919/1982	Fasciculations, atrophy, dysarthria. Normal reflexes and absent Babinski sign.	19	Personality change, poor hygiene.	Widespread denervation, low motor amplitudes	Cortical and central atrophy	Claudicatio intermittens
GL	M	1923/1993	Fasciculations, atrophy, increased reflexes and positive Babinski sign	24	Difficulties in ADL, poor memory	Widespread denervation, low motor amplitudes	Cortical and central atrophy	Abdominal aortic aneurysm
RL	M	1923/1983	Fasciculations, atrophy, decreased reflexes and absent Babinski sign.	20	No	Widespread denervation, low motor amplitudes	Normal	-
SL	M	1926/1994	No	-	Poor memory, concentration difficulties	ND	Cortical atrophy, Pons infarction	Operated abdominal aortic aneurysm. Died in myocardial infarction 1994
UG	W	1930/1997	No	-	No	ND	Left-sided cerebral infarction	Mitral valve prothesis. Atrial fibrillation. Died in heart insufficiency and cardiac arrest in 1997

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 capsula 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 prothesis 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 co-occurrence of family MND and frontotemporal dementia is well known [12]. This suggests that 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 claudicatio 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

1. Norum RA, Lakier JB, Goldstein S, Angel A, Goldberg RB, Block WD, Noffze DK, et al. Familial deficiency of apolipoproteins A-I and C-III and precocious coronary-artery disease. N Engl J Med. 1982;306(25):1513-1519.
2. Koren-Morag N, Goldbourt U, Graff E, Tanne D. Apolipoproteins B and AI and the risk of ischemic cerebrovascular events in patients with pre-existing atherothrombotic disease. J Neurol Sci. 2008;270(1-2):82-87.
3. Vollbach H, Heun R, Morris CM, Edwardson JA, McKeith IG, Jessen F, Schulz A, et al. APOA1 polymorphism influences risk for early-onset nonfamiliar AD. Ann Neurol. 2005;58(3):436-441.
4. Mulder DW, Kurland LT, Offord KP, Beard CM. Familial adult motor neuron disease: amyotrophic lateral sclerosis. Neurology. 1986;36(4):511-517.
5. Lomen-Hoerth C, Anderson T, Miller B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. Neurology. 2002;59(7):1077-1079.
6. Buee L, Perez-Tur J, Leveugle B, Buee-Scherrer V, Mufson EJ, Loerzel AJ, Chartier-Harlin MC, et al. Apolipoprotein E in Guamanian amyotrophic lateral sclerosis/parkinsonism-dementia complex: genotype analysis and relationships to neuropathological changes. Acta Neuropathol. 1996;91(3):247-253.
7. al-Chalabi A, Enayat ZE, Bakker MC, Sham PC, Ball DM, Shaw CE, Lloyd CM, et al. Association of apolipoprotein E epsilon 4 allele with bulbar-onset motor neuron disease. Lancet. 1996;347(8995):159-160.
8. Abarbanel JM, Frisher S, Osimani A. Primary amyloidosis with peripheral neuropathy and signs of motor neuron disease. Neurology. 1986;36(8):1125-1127.
9. Amarzguioui M, Mucchiano G, Haggqvist B, Westermark P, Kavlie A, Sletten K, Prydz H. Extensive intimal apolipoprotein A1-derived amyloid deposits in a patient with an apolipoprotein A1 mutation. Biochem Biophys Res Commun. 1998;242(3):534-539.
10. Selby G. Hereditary motor neuron disease. Clin Exp Neurol. 1987;24:145-151.
11. Hudson AJ. Amyotrophic lateral sclerosis and its association with dementia, parkinsonism and other

neurological disorders: a review. Brain. 1981;104(2):217-247.
12. Jackson M, Morrison KE, Al-Chalabi A, Bakker M, Leigh PN. Analysis of chromosome 5q13 genes in amyotrophic lateral sclerosis: homozygous NAIP deletion in a sporadic case. Ann Neurol. 1996;39(6):796-800.
13. Li YJ, Pericak-Vance MA, Haines JL, Siddique N, McKenna-Yasek D, Hung WY, Sapp P, et al. Apolipoprotein E is associated with age at onset of amyotrophic lateral sclerosis. Neurogenetics. 2004;5(4):209-213.
14. Zetterberg H, Jacobsson J, Rosengren L, Blennow K, Andersen PM. Association of APOE with age at onset of sporadic amyotrophic lateral sclerosis. J Neurol Sci. 2008;273(1-2):67-69.
15. Balasa M, Gelpi E, Antonell A, Rey MJ, Sanchez-Valle R, Molinuevo JL, Llado A. Clinical features and APOE genotype of pathologically proven early-onset Alzheimer disease. Neurology. 2011;76(20):1720-1725.
16. Mucchiano G, Cornwell GG, 3rd, Westermark P. Senile aortic amyloid. Evidence for two distinct forms of localized deposits. Am J Pathol. 1992;140(4):871-877.