Clinical characteristics of published cases of cerebellar syndrome from heat stroke

Patient	*Year*		*Age/sex*	*Temperature (°C)*	*Cause of fever*	*Clinical syndrome*	*Initial imaging*	*Recovery*	*Follow up imaging*
1	1970	Mehta and Baker[5]	47M	42.2	Confinement in heated cell	Hypotonia, intention tremor, ataxia, dysarthria	Unknown	None	CBLR atrophy
2	1987	Yaqub *et al*[6]	50F	43.2	Exertion in heat	Nystagmus, dysarthria, ataxia	CT NL	Nearly complete 5 months	CT at 5 months CBLR atrophy
3	1983	Lefkowitz *et al*[7]	50F	42.5	NMS	Ataxia, dysmetria, hypotonia	CT NL	None	CT NL
4	1995	Manto *et al*[8]	39M	41.6	NMS	Gait ataxia	CT NL	None 1 year	CT CBLR atrophy
5	1996	Manto[9]	44F	42.1	Exertion in heat	Dysarthria	CT NL	Complete 2 weeks	CT at 3 months normal
6	1996	Manto and Topka[10]	39F	41.1	Heat stroke	Gait ataxia	MRI NL	Complete 7 days	Not done
7	1996	Manto and Topka[10]	55M	40.9	Pneumonia	Gait ataxia	MRI NL	Complete 3 days	Not done
8	1996	Manto and Topka[10]	48F	40.7	Pyelonephritis	Gait ataxia	MRI NL	Complete 5 days	Not done
9	1996	Manto and Topka[10]	47M	40.7	Pneumonia	Gait ataxia	MRI NL	Complete 10 days	Not done
10	1996	Manto and Topka[10]	60M	40.8	Erysipelas	Gait ataxia	MRI NL	Complete 6 days	Not done
11	1997	Albukrek *et al*[11]	45M	42	Exertion in heat	Nystagmus, ataxia, dysarthria	CT NL	None	MRI at 10 weeks CBLR atrophy

NMS=neuroleptic malignant syndrome; CBLR=cerebellar; NL=normal..

1 Leigh J, Averbuch-Heller L. Nystagmus and related ocular motility disorders. In: Miller N, Newman NJ, eds. *Walsh and Hoyt's clinical neuro-ophthalmology, 5th ed.* Baltimore: Williams and Wilkins 1998:1472–3.
2 Takemori S, Suzuki M. Cerebellar control to oculomotor function. *Otorhinolaryngology* 1977;**39**:209–17.
3 Takemori S, Cohen B. Loss of visual suppression of vestibular nystagmus after flocculus lesions. *Brain Res* 1974;**72**:213–24.
4 Khosla R, Guntapalli R. Heat related illnesses. *Crit Care Clin* 1999;**15**:251–63.
5 Mehta AC, Baker RB. Persistent neurologic deficits in heat stroke. *Neurology* 1970;**20**:336–40.
6 Yaqub BA, Daif AK, Panyaoitoulos CP. Pancerebellar syndrome in heat stroke: clinical course and CT scan findings. *Neuroradiology* 1987;**29**:294–6.
7 Lefkowitz D, Ford CS, Rich C, *et al*. Cerebellar syndrome following neuroleptic induced heat stroke. *J Neurol Neurosurg Psychiatry* 1983;**46**:183–5.
8 Manto M, Goldman S, Hildebrand J. Cerebellar ataxia following NMS. *J Neurol* 1996;**243**:101–2.
9 Manto M. Isolated cerebellar dysarthria associated with heat stroke. *Clin Neurol Neurosurg* 1996;**98**:55–6.
10 Manto M-U, Topka H. Reversible cerebellar gait ataxia with postural tremor during episodes of high pyrexia. *Clin Neurol Neurosurg* 1996;**98**:227–30.
11 Albukrek D, Bakon M, Moran DS, *et al*. Heat-induced cerebellar atrophy: clinical course, CT and MRI findings. *Neuroradiology* 1997;**39**:195–7.
12 D'souza C, Rush S, Brown I. Effect of hyperthermia on the transcription rate of heat shock genes in the rabbit cerebellum and retina assayed by nuclear run-ons. *J Neurosci Res* 1998;**52**:538–48.

Apolipoprotein E ε2 may be a risk factor for sporadic frontotemporal dementia

Frontotemporal dementia (FTD) is the second most common form of presenile dementia, after early onset Alzheimer's disease. Up to half of cases of FTD are thought to be familial, probably with an autosomal dominant mode of inheritance, some with mutations on chromosome 17. The genetics of sporadic FTD have been less studied, although several groups have examined the potential association of FTD with apolipoprotein E (APOE) ε4, with inconclusive results.[1–3]

We studied 11 patients with sporadic FTD (excluding patients with first degree relatives with dementia) in the cohort of the Oxford project to investigate memory and aging (OPTIMA). Nine of the 11 were histopathologically confirmed and the remaining two fulfilled the consensus criteria of Neary *et al*[4] (three of the first nine had also been clinically diagnosed by these criteria and all three were confirmed at necropsy); only one of the nine confirmed cases was Pick-type. Apolipoprotein E genotyping was performed, blind to diagnosis, by polymerase chain reaction methods[5] for the 11 patients with FTD (mean age at death or last examination: 65.7 years; six women) and for 136 elderly controls (mean age: 77.5 years; 77 women), without cognitive impairment and with CAMCOG scores greater than 80, from the OPTIMA cohort. An older control group was used to minimise the chance inclusion of future cases of FTD; APOE allele frequencies did not vary with age in our controls. Controls and patients were Caucasians from the Oxford region. Genotyping results are shown in the table.

Allele frequencies of APOE in cases of FTD versus controls, respectively, were: 0.32 versus 0.06 for APOE ε2, 0.64 versus 0.78 for APOE ε3, and 0.05 versus 0.16 for APOE ε4. The one Pick-type case was an APOE ε2/ε3 heterozygote. We did not have enough cases of FTD to distinguish between allele frequencies of predominantly frontal and mainly temporal cases. Control frequencies were similar to those widely reported for Caucasians. All control and FTD genotypes were in Hardy-Weinberg equilibrium. The above allele frequencies yielded odds ratios of FTD of 7.0 (95% confidence interval (95% CI) 2.5–19.5, p=0.0007) for APOE ε2, of 0.50 (p=0.18, NS) for APOE ε3, and of 0.25 (p=0.22, NS) for APOE ε4, suggesting that APOE ε2 could be a risk factor for FTD.

We examined eight previous reports[1–3 6] with APOE genotypes of cases of FTD and controls. This showed that seven of the eight had APOE ε3 odds ratios of FTD less than 1, as in our study, consistent with a protective association, whereas results for APOE ε2 and for APOE ε4 were highly varied. Frequencies of APOE ε2 in FTD ranged from zero[6] to a significant excess noted by Gustafson *et al*.[2] We suggest that these contrasting results are due to differences in diagnostic and exclusion criteria. Not all reports specified their diagnostic criteria and four of the eight were based solely on clinical diagnosis of FTD, which admits the possible inclusion of concomitant or misdiagnosed Alzheimer's disease, especially if NINCDS-ADRDA criteria are used.[7] Including cases of Alzheimer's disease would be expected to raise the APOE ε4 frequency and to lower that of APOE ε2. Perhaps more importantly, only two studies[2 3] of the eight excluded or separated familial cases.

Table 1 Apolipoprotein E genotypes in sporadic frontotemporal dementia (FTD) and in elderly controls in OPTIMA

	Apolipoprotein E genotypes					
Subjects (n)	*2/2*	*2/3*	*2/4*	*3/3*	*3/4*	*4/4*
FTD (11)	—	6	1	4	—	—
Controls (136)	—	11	6	83	35	1

Our suggestions, that APOE ε2 may be a risk factor for sporadic FTD and APOE ε3 might be protective, need to be investigated in a larger, probably collaborative study. Strict diagnostic and exclusion criteria should be used. We propose the inclusion only of histopathologically confirmed cases or of those fulfilling the consensus criteria of Neary *et al* 1998[4] (list 1 or 2, FTD or progressive non-fluent aphasia), strictly applied, and the exclusion of cases with first degree relatives with dementia, or with signs of parkinsonism at an early stage, or of corticobasal degeneration.

If it is indeed shown that APOE ε2, although protective against late onset Alzheimer's disease, is a risk factor for sporadic FTD, this will provide a new insight into mechanisms of risk and protection related to APOE in both diseases.

Since submitting this letter, we have read an important and relevant report by the Manchester group,[8] easily the largest and most comprehensive study to date on APOE frequencies in FTD and related disorders. The group examined 35 controls and 163 patients, including 58 with FTD without family history, and found no association of any APOE allele with FTD. Their APOE ε2 allele frequencies were 0.06 in controls, similar to ours, and 0.09 in non-familial cases of FTD. When pooling their data with ours, however, we obtained APOE ε2 frequencies of 0.12 in sporadic FTD (n=69) and 0.06 in controls (n=171). This gave an odds ratio of sporadic FTD for that allele of 2.15 (95% CI 1.1–4.2, p=0.04).

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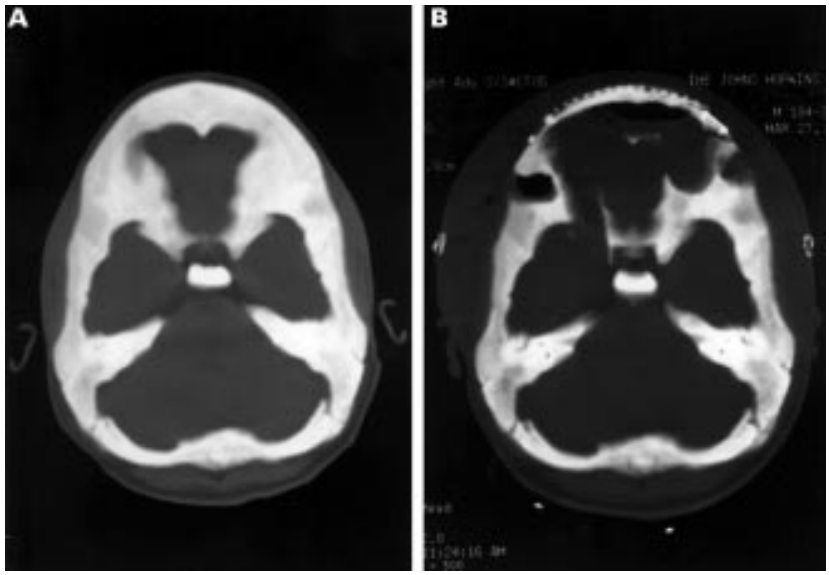
1 Pickering-Brown SM, Siddons M, Mann DMA, *et al*. Apolipoprotein E allelic frequencies in patients with lobar atrophy. *Neurosci Lett* 1995;**188**:205–7.
2 Gustafson L, Abrahamson M, Grubb A, *et al*. Apolipoprotein-E genotyping in Alzheimer's disease and frontotemporal dementia. *Dement Geriatr Cogn Disord* 1997;**8**:240–3.
3 Stevens M, van Duijn CM, de Knijff P, *et al*. Apolipoprotein E gene and sporadic frontal lobe dementia. *Neurology* 1997;**48**:1526–9.
4 Neary D, Snowden JS, Gustafson L, *et al*. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;**51**: 1546–54.
5 Wenham PR, Price WH, Blandell G. Apolipoprotein E genotyping by one-stage PCR. *Lancet* 1991;**337**:1158–9.
6 Helisalmi S, Linnaranta K, Lehtovirta M, *et al*. Apolipoprotein E polymorphism in patients with different neurodegenerative disorders. *Neurosci Lett* 1996;**205**:61–4.
7 Varma AR, Snowden JS, Lloyd JJ, *et al*. Evaulation of the NINCDS-ADRDA criteria in the differentiation of Alzheimer's disease and frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 1999;**66**:184–8.
8 Pickering-Brown SM, Owen F, Isaacs A, *et al*. Apolipoprotein E ε4 allele has no effect on age at onset or duration of disease in cases of frontotemporal dementia with Pick- or microvacuolar-type histology. *Exp Neurol* 2000; **163**:452–6.



Non-enhanced CT, axial view, with bone window settings, before and after decompression of the right optic canal and cranial vault expansion. (A) Preoperative scan shows marked thickening of the calvarium. The optic canals are narrowed by the diffusely thickened bone. (B) Postoperative scan shows that the right optic canal has been completely unroofed. Note that the decompression extends well into the orbital apex. Anterior cranial vault expansion can also be appreciated.

Bilateral visual improvement after unilateral optic canal decompression and cranial vault expansion in a patient with osteopetrosis, narrowed optic canals, and increased intracranial pressure

Osteopetrosis (Albers-Schonberg disease, marble bones) is a relatively rare disease that is characterised by increased skeletal mass and bone density.[1] It results from a defect in the development or function of osteoclasts with consequent impairment of bone resorption. The defect may be intrinsic to the osteoclast lineage or the mesenchymal cells that support the development and activation of the osteoclasts. Osteopetrosis is inheritable, and four clinical forms have been distinguished: autosomal-recessive malignant, autosomal-dominant benign, mild autosomal-recessive, and autosomal-recessive osteopetrosis with renal tubular acidosis. Of the four, the first two are the most prevalent.[1] The disease is characterised clinically by multiple fractures, abnormally shaped bone, and anaemia. Its neurological manifestations include cerebrovascular complications, cranial nerve palsies, papilloedema, and blindness from optic nerve atrophy.[2–5] Optic nerve atrophy is common and can result from the chronic effects of papilloedema or compression by a narrowed optic canal. Optic neuropathy associated with papilloedema can be prevented by aggressive management of intracranial pressure (ICP), whereas that associated with narrowing of the optic canal is usually treated by neurosurgical decompression.[4 5]

A 19 year old man, diagnosed with autosomal recessive osteopetrosis at about 5 months of age, presented in March 1997 with a dramatic decline in vision. He previously had had visual acuity of 20/30 in his right eye, 20/50 in his left eye, and full visual fields for most of his life. A brain CT in 1986 showed no optic canal narrowing. In 1994, he developed increased ICP and underwent a left optic nerve sheath fenestration and placement of a lumboperitoneal shunt (LPS). His vision remained normal until August of 1996 when he began to experience declining vision. He was referred to the Johns Hopkins Hospital in March of 1997.

Visual acuity with correction was 20/200 in each eye. Near vision was 20/400 in each eye. Visual fields were limited in each eye to a tiny paracentral area of about 5 degrees. Colour vision was markedly impaired, with the patient being unable to identify any of the figures on the Hardy-Rand-Rittler (HRR) pseudoisochromatic plates. Pupils were equal and reactive to light, and there was a left relative afferent pupillary defect of 0.3 log units when measured using a neutral density filter. Extraocular movements were normal. Ophthalmoscopy disclosed bilaterally pale optic discs.

Non-contrast CT of the head showed marked diffuse thickening of the calvarium with a ground glass appearance. The bony dysplasia involved the skull base, and there was narrowing of both optic canals, the petrous carotid canals, the internal auditory canals, and the cochlear and vestibular apparatus (figure A). There was also ossification of the mastoid and frontal sinuses. The CT also showed evidence of increased ICP, including an effaced third ventricle. An indium radiotracer study showed that the LPS catheter was patent, but ultrasonography demonstrated bilateral enlargement of the retrobulbar optic nerves and a positive 30 degree test, consistent with increased ICP, and a lumbar puncture disclosed an opening pressure of 450 mm Hg, with normal CSF contents.

Consideration was given to treating the patient with acetazolamide, but because of the severity of visual loss associated with pale optic discs, and because it was unclear if his decreased visual function was caused by compression of the optic nerves by the narrowed optic canals or increased ICP, it was decided to perform bilateral non-simultaneous optic canal decompressions combined with a cranial vault expansion. A bicoronal incision was made, a full thickness scalp flap was turned down to the level of the superior orbital rims bilaterally, and a large bifrontal bone flap was removed. The roof of the right optic canal was then removed along its entire length using a high speed drill and curettes. The bone flap, which was 3 cm thick, was thinned to about 1 cm and replaced, producing a significant cranial expansion.

Four days after surgery, the patient's visual acuity had improved to 20/30 bilaterally, he could correctly identify figures on seven of 10 HRR plates with the right eye and six of 10 colour plates with the left eye, and his visual fields were markedly expanded, almost to normal. A postoperative CT confirmed complete unroofing of the right optic canal (figure B).

Osteopetrosis related visual loss is often ascribed to optic nerve compression secondary to the narrowing of the optic foramina. However, optic nerve dysfunction can also result from the effects of increased ICP. Because our patient's unilateral optic canal decompression resulted in bilateral improvement in visual acuity and visual fields, it is reasonable to conclude that increased ICP and not narrowing of the optic canals was the cause of his visual deterioration. Thus, the cranial vault expansion that was performed in addition to the unilateral optic canal decompression was responsible for the rapid and dramatic improvement in the patient's visual function.

This case provides an important lesson on the evaluation of any patient with optic neuropathy that is presumed to be secondary to narrowing of optic canals in the setting of one of the craniostenoses. Although direct compression may indeed be primarily responsible for visual deterioration in patients with osteopetrosis and related conditions, increased ICP, related to either thickening of the skull or secondary occlusion of one of the cerebral venous sinuses, should always be considered a potential aetiology, and aggressively treated when identified or suspected.

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