Genotype and allele frequency of APOE in patients with late onset Alzheimer's disease (LOAD), controls, and general population in Argentina

Group (n)	Mean age (y)	2/2	2/3	2/4	3/3	3/4	4/4	ε2	ε3	ε4
LOAD (45)	74·72	0	0	0	28	14	3	0 (0)	0·62 (70)	0·22 (20)*
Controls (45)	71·89	0	1	0	37	7	0	0·011 (1)	0·911 (82)	0·077 (7)
General population (101)	33·81	0	5	7	65	24	0	0·059 (12)	0·787 (159)	0·153 (31)

*P = 0·015 (Fisher's exact statistics), LOAD *v* controls.
Allele numbers are in parenthesis.

tively low ε4 frequency in patients with late onset Alzheimer's disease and controls. It is important to notice that we only had two patients with Alzheimer's disease considered as familial late onset (both carrying one ε4 allele). Previous studies have shown that if the proportion of familial cases increases in the sample, the relative ε4 frequency is higher.[3] On the other hand, the criteria used to classify a patient with Alzheimer's disease as being familial or sporadic are not homogeneous among different studies, so it is possible that our criteria for sporadic patients were more stringent than those used by other authors. This interpretation may explain, at least partially, why our ε4 allele frequency in Alzheimer's disease is one of the lowest reported so far. The lower ε4 frequency in our control group than the young general population can be explained considering that selection against age among ε4 allele carriers may take place in our country at an earlier age compared with other countries. It has been reported that the age adjusted mortality for coronary heart disease in Argentina is one of the highest in the world for both sexes in the age group 35–64 years (36·12% for men and 33·4% for women) and that the risk increases proportionally with age.[5] Although this unusually high cardiovascular mortality in our country can be related to a high cholesterol diet, smoking, hypertension, or diabetes, there is no information available regarding the influence of the ε4 allele, a well known risk factor for coronary artery disease. Therefore, it remains possible that the inheritance of the ε4 allele is a strong determinant of cardiovascular mortality in our community resulting in its low frequency in the age group at risk for Alzheimer's disease. Further epidemiological studies will clarify this issue. The reported possible protective effect of the ε2 allele in late onset Alzheimer's disease could not be evaluated due to the insufficient size of our sample for this purpose.

In conclusion, our results corroborate the association between the ε4 allele and late onset Alzheimer's disease in the Hispanic population from South America, as has been shown in other populations with different ethnic backgrounds. The allele is overexpressed almost three times in the affected persons and the OR value is in general agreement with previous reports regardless of the relatively low frequencies of ε4 alleles among patients with Alzheimer's disease and controls found in our study. Moreover, the lack of a significant difference in the ε4 allele frequency between the Alzheimer's disease group and our young population underscores the importance of case-control studies in communities with a high cardiovascular mortality in the age group younger than 64 years for the evaluation of the ε4 allele as a risk factor for late onset Alzheimer's disease.

We thank Maria Lujan Calcagno for her assistance in statistic analysis. The work was supported in part by grants of CONICET and UBA (FA 111).

LAURA MORELLI
JULIAN LEONI
EDUARDO M CASTAÑO
Department of Microbiology, Immunology and Biotechnology, University of Buenos Aires, Argentina.
CARLOS A MANGONE
Neurology Section and Dementia Research Centre Santojanni Hospital, Buenos Aires, Argentina
ALBERTO LAMBIERTO
Sanatorio Otamendi, Buenos Aires, Argentina

Correspondence to: Dr Laura Morelli, Department of Microbiology, Immunology and Biotechnology, University of Buenos Aires, Junin 956 4th floor (1113) Capital Federal, Argentina.

1 Saunders AM, Strittmatter WJ, Schmechel DE, *et al.* Association of apolipoprotein E allele ε4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993;**43**: 1467–72.
2 Adroer R, Santacruz P, Blesa R, López-Pousa S, Ascaso C, Oliva R. Apolipoprotein ε4 allele frequency in Spanish Alzheimer and control cases. *Neurosci Lett* 1995;**189**:182–6.
3 Lannfelt L, Lilius L, Nastase M, *et al.* Lack of association between apolipoprotein E allele ε4 and sporadic Alzheimer's disease. *Neurosci Lett* 1994;**169**:175–8.
4 Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with Hha I. *J Lip Res* 1990;**31**:545–8.
5 Balossi EC and Hauger-Klevene JH. Mortalidad por enfermedad isquémica coronaria en la Argentina (1962–1978): su relación con los factores de riesgo cardiovascular. *Rev Arg Cardiol* 1987;**55**:196–200.

Systematic overestimation of intracranial pressure measured using a Camino pressure monitor

The Camino fibreoptic intracranial pressure (ICP) monitor (Camino Laboratories, San Diego, CA, USA) was the first intraparenchymal microtransducer to be used widely in clinical practice. Recent laboratory tests[1] have confirmed its excellent accuracy and low long term drift when temperature remained constant. However, an increase in ambient temperature pro-

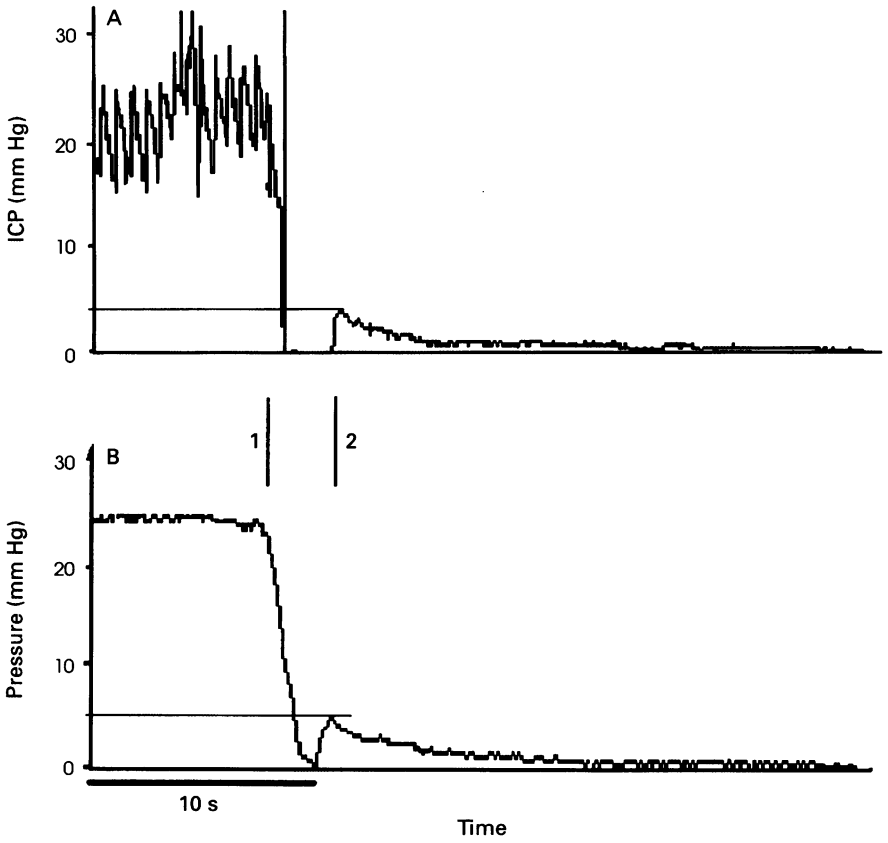

Figure 1 (A) Recording of ICP during removal of a Camino transducer from the subarachnoid space of patients with head injury. The transducer was removed at time point 1. Readings were unstable for about three seconds and then the temperature drift from 4 mm Hg (starting at time point 2) to 0 mm Hg was recorded during cooling of the catheter tip to room temperature. (B) A similar effect to point A was recorded during removal of a Camino transducer submerged in a cylinder filled with warm water (36°C). The pressure decreased (time point 1) from around 25 mm Hg (height of water column) over one second to 0 mm Hg. It is hypothesised that this deeper than expected decrease is caused by an immediate cooling during vaporisation of the water from a wet membrane—too small to cool the whole catheter tip. It is repeatable and is probably equivalent to the period of "unstable reading" seen in A. The pressure then increased to 5 mm Hg (at time point 2) and subsequently decreased gradually to 0 mm Hg over the next 20 seconds.

duced a positive drift as high as 0·27 mm Hg/°C.

This has important practical implications as the transducer is usually zeroed at room temperature (18–21°C) before insertion in the subarachnoid space (36–38°C). Hence the displayed value of ICP is as much as 4–5 mm Hg higher than the true ICP. One way to show this effect in clinical practice is to monitor the pressure signal during removal of the microtransducer from the patient's brain. The pressure waveform disappears immediately (figure, A—point 1) and the reading falls rapidly (commonly after a 5–10 second period of unstable reading) to around 4–5 mm Hg. There is then a more gradual decrease to 0 mm Hg over the next 10–20 seconds. This decrease represents the temperature drift during cooling of the membrane to room temperature. A similar temperature drift can be easily shown by removing the Camino catheter tip from a glass of warm water (figure, B).

The 4–5 mm Hg offset is perhaps of little importance in patients with normal ICP, but it is relevant when active treatment of raised ICP is introduced over a critical threshold (for example, ICP above 25 mm Hg). Statistical assessment of the predictive value of various levels of ICP and cerebral perfusion pressure should be based on values corrected for the offset of Camino transducers.

MAREK CZOSNYKA
SPENCER HARLAND
STEFAN PIECHNIK
PETER KIRKPATRICK
Neurosurgery Unit
ZOFIA CZOSNYKA
Department of Health Shunt Evaluation Laboratory
DAVID MENON
Department of Anaesthesia, Addenbrooke's Hospital, Cambridge, UK

Correspondence to: Dr M Czosnyka, Academic Neurosurgical Unit, Addenbrooke's Hospital, PO Box 167, Cambridge CB2 2QQ, UK.

1 Czosnyka M, Czosnyka Z, Pickard JD. Laboratory testing of three intracranial pressure microtransducers—a technical report. *Neurosurgery* 1996;**38**:219–24.

Intracranial mucoceles with midline fusion defects

We report a patient with large bifrontal intracranial mucoceles presenting with seizures and progressive mental deterioration. The diagnosis was only confirmed after operative intervention. Midline congenital malformations of bifid nasal septum, submucosal bifid uvula, and subcutaneous nasal fistula were also subsequently documented.

Mucoceles, usually associated with paranasal sinuses can be defined as an abnormal accumulation and retention of mucous secretions. They tend to present with intraorbital or paranasal symptomatologies but rarely with purely neurological symptoms.[1] This case report illustrates one such patient who has in addition, evidence of other midline congenital malformations.

The patient, a white man, first presented in June 1987 at the age of 32 years to the Department of Neurology after two grand mal seizures. He had no history of infection, trauma, or operation involving the cranium, face, or paranasal sinuses. He denied any other symptoms. There was a positive family history for epilepsy (patient's brother) and nasal sinusitis. His initial physical examination did not disclose any focal neurological abnormality. Skull radiographs and EEG were reported as normal. He was managed with a provisional diagnosis of epilepsy of idiopathic origin.

Seizure control remained poor despite individual trials with phenytoin, sodium valporate, and carbamazepine. As a result of a further increase in seizure frequency after October 1989, he underwent CT of his brain (fig 1A). This showed bilateral frontal non-contrast enhancing hyperdense lesions with no surrounding oedema. Coronal CT (fig 1B) showed that these lesions arose from the anterior cranial fossa floor. Magnetic resonance imaging showed low signals on both T1 and T2 weighted images.

On referral to the Department of Neurosurgery, operative intervention was deferred as his only symptom was seizures and the risks of surgically induced bifrontal lobe damage was considered to be unwarranted. He remained under the care of the neurologists to control his seizures, which occurred about once a month.

He was rereferred in 1993 with a history of gradually progressive lethargy and apathy. His relatives noted abnormal behaviour and neglect of his personal hygiene. Subsequent physical examination disclosed bilateral papilloedema and a repeat brain CT showed a further increase in the lesion size. Radiological angiographical studies did not show any significant vascular supply to the tumour.

The patient underwent a bicoronal flap and frontal craniotomy in October 1993. The surface of the brain was normal. A cystic lesion was encountered at a depth of 1 cm containing thick, dark brown mucous-like material. Aspiration on the right side led to collapse of both frontal lobes confirming the intercommunication between the two lobes. After the aspiration of all the cystic contents, fibrin sealant (Tisseel®, Immuno AG, Vienna, Austria) was injected into the base of the cyst with the aim of sealing off any potential communication with the ethmoidal sinuses. Immediate histological smear of the contents showed acellular material with keratin. Paraffin section of the biopsy of the wall showed gliotic tissue lined by epithelium on a thin layer of collagen. The epithelium was multilayered and columnar (respiratory sinus epithelium?) with no ciliated or goblet cells suggesting squamous differentiation. Bacteriological studies showed the cystic contents to be sterile.

Postoperative recovery was uneventful and CT of the brain one week later showed complete evacuation of the mucoceles (fig 1C). He subsequently underwent ear, nose, and throat assessment at which a midline nasal hairy punctum was noted (fig 2), with an underlying track extending at least 3 cm in the subcutaneous layer in a superior direction towards the glabella. He also had a submucosal bifid uvula. Radiological studies showed this tract to be blind ending in the subcutaneous tissues with no obvious intracranial communication. A further review of the previous imaging showed a bifid nasal septum and an aerated crista galli. The above findings were consistent with congenital midline fusion defects.

In this patient, mucocele recurrence is anticipated as the walls were not completely excised. Further neurosurgical intervention possibly in combination with the repair of the anterior cranial fossa floor, external rhinoplasty, and excision of the midline tract may be necessary to prevent further recurrence. No attempt would be made to com-

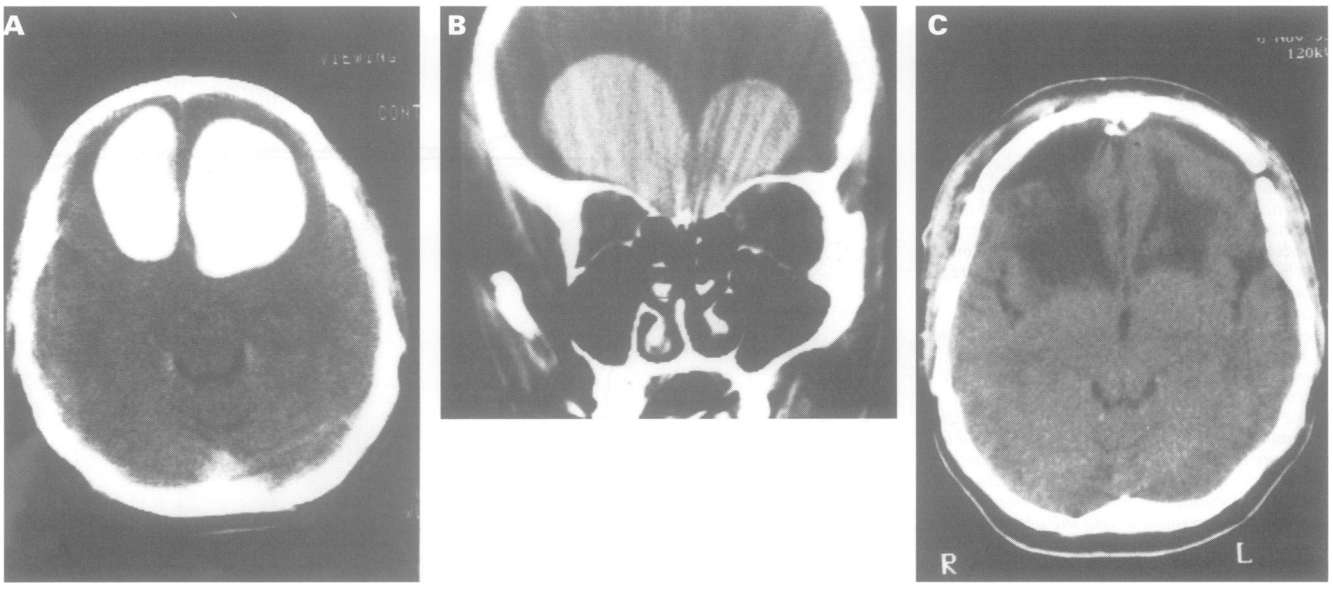

Figure 1 (A) Axial cranial CT (1989) showing the bilobed frontal hyperdense lesions. (B) Coronal cranial CT (1989) showing the communication of the lesions from the floor of the anterior cranial fossa. (C) Postoperative axial cranial CT (1993).