

cidental infection or the non-specific elevation of the antibody titre due to polyclonal activation of the memory B cells, there remains a possibility that this virus triggered the immunological derangement of this unusual case.

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#### References

- Behan PO, Lowenstein LM, Stilmant M, Sax DS. Landry-Guillain-Barré-Strohl syndrome and immune complex nephritis. *Lancet* 1973;i:850-4.
- Peters DK, Sevvitt LH, Direkze M, Bayliss SG. Landry-Guillain-Barré-Strohl polyneuritis and the nephrotic syndrome. *Lancet* 1973;i:1183-4.
- Grover RW. Transient acantholytic dermatosis. *Arch Dermatol* 1970;101:426-34.
- Bystryn J. Immunofluorescence studies in transient acantholytic dermatosis (Grover's disease). *Am J Dermatopathol* 1979;1:325-7.
- Atkins DK, Kondon Jr JJ, Quismorio FP, Friou GJ. The choroid plexus in systemic lupus erythematosus. *Ann Intern Med* 1972;76:65-72.
- Koss MN, Chernack WJ, Griswold WR, McIntosh RM. The choroid plexus in acute serum sickness. Morphologic, ultrastructural, and immunohistologic studies. *Arch Pathol* 1973;96:331-4.
- Grundke-Iqbal I, Lassmann H, Wisniewski HM. Chronic relapsing experimental allergic encephalomyelitis. Immunohistochemical studies. *Arch Neurol* 1980;37:651-6.

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#### Visual evoked potentials and neopterin: biopterin ratios in urine show a high correlation in Alzheimer's disease

Sir: Tetrahydrobiopterin is the rate controlling co-factor in the synthesis of the neurotransmitters dopamine and noradrenaline.<sup>1</sup> Alzheimer's disease is associated with decreased tetrahydrobiopterin levels,<sup>2-5</sup> through the reduced conversion of dihydroneopterin triphosphate to tetrahydrobiopterin.<sup>6</sup> Analysis of postmortem cerebrospinal fluid,<sup>7</sup> postmortem temporal cortex<sup>4</sup> and serum of patients<sup>8</sup> with Alzheimer's disease has shown that an

elevated neopterin: biopterin (N:B) ratio is a measure of this reduced conversion rate.

In Alzheimer's disease, measurement of the visual evoked potential (VEP) has shown that the major positive, or P2, component of the flash VEP is delayed, while the P100 component of pattern reversal VEP is unaffected.<sup>9,10</sup> This unusual combination of results is believed to indicate that the pathology is at the level of the visual association areas. Subtraction of the latency of the pattern reversal P100 component from the flash P2 component, therefore gives a value which is elevated in Alzheimer's disease. The magnitude of this flash-pattern latency difference has been shown to increase with increasing severity of dementia.<sup>10,11</sup>

Ten patients suffering from Alzheimer's disease were diagnosed and referred for the study by a consultant psychogeriatrician. All were diagnosed as presenting with primary dementia of the Alzheimer type with no evidence of cerebrovascular disease. All had significant memory loss but were capable of fixating pattern reversal stimulus and providing a urine sample. The degree of dementia was moderate. Urine samples, taken directly into ascorbic acid to give a final ascorbate concentration of 1%, were measured for neopterin, biopterin and creatinine.<sup>12</sup> Flash and pattern visual evoked potentials (VEPs) were recorded.<sup>10</sup> The mean age of the patients was 77.7 years (standard deviation 8.21 years). The nine controls were paid volunteers, with a mean age of 81 years (standard deviation 4.39 years) with a binocular visual acuity of 6/9 or better and a Royal College of Physicians mental test score of 29/34 or better.<sup>13,14</sup> Ophthalmoscopy was carried out on all patients and controls and a medical history obtained. No one with evidence of ophthalmic pathology or diseases affecting the immune system was included as these would affect the pattern VEP and neopterin: biopterin ratios respectively.

The table shows that the mean values of N:B ratio, flash P2 latency and flash-pattern difference were all significantly elevated in the group with Alzheimer's disease compared with the controls. The relationship between the urine and VEP results was investigated by the determination of the cor-

relation coefficient. There is a highly significant correlation between the urine N:B ratio and both flash P2 latency and the flash-pattern difference (table).

The correlation between the N:B ratios and the VEP measures shows that with increasing disease severity there is decreasing conversion of dihydroneopterin triphosphate to tetrahydrobiopterin.

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#### References

- Leeming RJ, Pheasant AE, Blair JA. The role of tetrahydrobiopterin metabolism in neurological disease: A review. *J Ment Deficit Res* 1981;25:231-41.
- Leeming RJ, Blair JA. The effects of pathological and normal physiological processes on biopterin derivative levels in man. *Clin Chim Acta* 1980;108:103-11.
- Aziz AA, Leeming RJ, Blair JA. Tetrahydrobiopterin metabolism in senile dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry* 1983;46:410-3.
- Barford PA, Blair JA, Eggar CS, Hamon CGB, Morar C, Whitburn SB. Tetrahydrobiopterin metabolism in the temporal lobe of patients dying with senile dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry* 1984;47:736-8.
- Williams AC, Levine RA, Chase TN, Lovenberg W, Calne DB. CSF hydroxylase co-factor levels in some neurological diseases. *J Neurol Neurosurg Psychiatry* 1980;43:735-8.
- Anderson JA, Hamon CGB, Armstrong RA, Blair JA. Tetrahydrobiopterin metabolism in normal brain, senile dementia of the Alzheimer type and Down's syndrome. In: Cooper B, Whitehead V, Walter de Gruyter, eds. *Chemistry and Biology of Pteridines*. Berlin: 1986:327-30.
- Morar C, Whitburn SB, Blair JA, Leeming RJ, Wilcock GK. Tetrahydrobiopterin metabolism in senile dementia of the Alzheimer type.

	N:B ratio	Flash P2 latency (ms)	Flash P2-pattern P100 difference (ms)
Alzheimer's disease (±SD) n = 10	2.43 ± 1.56	156.7 ± 17.1	60.4 ± 7.8
Control group (±SD) n = 9	1.51 ± 0.62	136.6 ± 7.3	31.4 ± 9.9
T test: statistical significance	p < 0.05	p < 0.01	p < 0.002
Correlation with N:B ratios		0.83(p < 0.01)	0.92(p < 0.001)

*J Neurol Neurosurg Psychiatry* 1983;46:582-90.

- 8 Young JH, Kelly B, Clayton BE. Reduced levels of bioppterin and dihydropteridine reductase in Alzheimer-type dementia. *J Clin Exp Gerontol* 1982;4:389-402.
- 9 Wright CE, Harding GFA, Orwin A. Presenile dementia—the use of the flash and pattern VEP in diagnosis. *Electroencephalogr Clin Neurophysiol* 1984;57:405-15.
- 10 Harding GFA, Wright CE, Orwin A. Primary presenile dementia: the use of the visual evoked potential as a diagnostic indicator. *Br J Psychiatry* 1985;147:532-9.
- 11 Orwin A, Wright CE, Harding GFA, Rowan DC, Rolfe EB. Serial visual evoked potential recordings in a case of Alzheimer's disease. *Br Med J* 1986;293:9-10.
- 12 Fukushima T, Nixon JC. Analysis of reduced forms of bioppterin in biological tissues and fluids. *Anal Biochem* 1980;102:176-8.
- 13 Silver CP. Test for assessment of mental function. *Age Ageing* 1978;7:12-16 (supplement).
- 14 Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry* 1968;114:797-811.

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#### Paradoxical reversal of ptosis in myasthenia gravis by edrophonium administration

Sir: Paradoxical responses, worsening and reversal of ptosis, in myasthenia gravis can sometimes be seen following administration of edrophonium chloride (Tensilon), but their precise mechanisms are not fully understood.<sup>1,2</sup> We report two patients with ocular myasthenia gravis whose ptosis reversed paradoxically by the intravenous administration of edrophonium, and discuss the possible mechanisms.

*Patient 1*, a 44 year old woman, had a left severe ptosis which developed about a year after thymectomy. Both anti-acetylcholine receptor (AChR) antibody and anti-striational antibody tests were positive. Early in the morning she always found her right eyelid transiently ptotic, which later in the day became seemingly normal, and left severe persistent ptosis developed.

We also confirmed such a spontaneous reversal of ptosis even during examination. Neurological examination did not reveal other muscle weakness except for that of the left eyelid closure. The intravenous administration of 5 mg edrophonium resulted in a paradoxical reversal of ptosis. The elevation of the eyebrow was also reversed (fig). She did not receive any anticholinesterase medication.

*Patient 2* was an 11 year old girl who had developed left ptosis, diplopia and photophobia since the age of 5 years. Neurological examination at the time of onset revealed bilateral ptosis and left pseudointernuclear ophthalmoplegia. These signs were relieved by edrophonium injection. Furthermore, the cold test<sup>3</sup> also alleviated her ptosis. Prednisolone therapy (20 mg every other day) improved her ocular symptoms moderately. At the age of 11 an exacerbation of left ptosis and limited ocular movement developed following physical exertion. She was aware that her right eyelid was ptotic when she awoke in the morning and that soon after the ptosis shifted from right to left spontaneously. By the intravenous administration of 2 mg edrophonium, her left eyelid became rather retracted and her ptosis shifted from left to right. She did not receive any anticholinesterase medication. The intravenous methylprednisolone pulse therapy led to a marked improvement of her ocular abnormalities.

Worsening of ptosis after the injection of edrophonium has generally been considered to be a negative response.<sup>1</sup> Reversal of ptosis was interpreted as follows: the ptotic eyelid developed retraction and the normal eyelid became ptotic.<sup>2</sup> In our patients, however, the eyelid which became ptotic after the edrophonium injection was not normal but was the affected one which drooped early in the morning and after a short sleep. Spontaneous shift of ptosis could be explained by Hering's law of bilateral and equal levator innervation:<sup>4</sup> fatigability of one eyelid was greater than that of the other, thus resulting in persistent ptosis of one eye and

the other eyelid became seemingly normal because of the central compensation for the ptosis.

When the edrophonium test was performed at this point, its effect was more prominent on the eyelid with an active lesion, leaving the other eyelid with a relatively inactive lesion ptotic. The edrophonium-induced eyelid retraction in patient 2, possibly associated with increased presynaptic ACh release to compensate for the impaired AChR<sup>5</sup> prior to the test, may partially be responsible for the contralateral eyelid descent by Hering's law. The ptosis of our patients was not induced by an overdose of anticholinesterase since they received no oral anticholinesterase medication. We believe that the present observation may provide one of the plausible explanations for the edrophonium-induced reversal of myasthenic ptosis.

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#### References

- 1 Miller NR. Myopathy and disorders of neuromuscular transmission: congenital and acquired disorders affecting the neuromuscular junction. In: *Walsh and Hoyt's Clinical Neuro-Ophthalmology* vol 1. Baltimore: Williams & Wilkins Co., 1982:851-2.
- 2 Burde RM, Savino PJ, Trobe JD. Diplopia: Myasthenia gravis. *Clinical Decisions in Neuro-Ophthalmology*. St. Louis: The C.V. Mosby Co., 1985:175-8.
- 3 Saavedra J, Femminini R, Kochen S, et al. A cold test for myasthenia gravis. *Neurology* 1976;29:1075.
- 4 Gay AJ, Salmon ML, Windsor CE. Hering's law, the levators, and their relationship in disease states. *Arch Ophthalmol* 1967;77:157-60.
- 5 Cull-Candy SG, Miledi R, Trautmann A, et al. On the release of transmitter at normal, myasthenia gravis and myasthenic syndrome affected human end-plates. *J Physiol (Lond)* 1980;299:621-38.

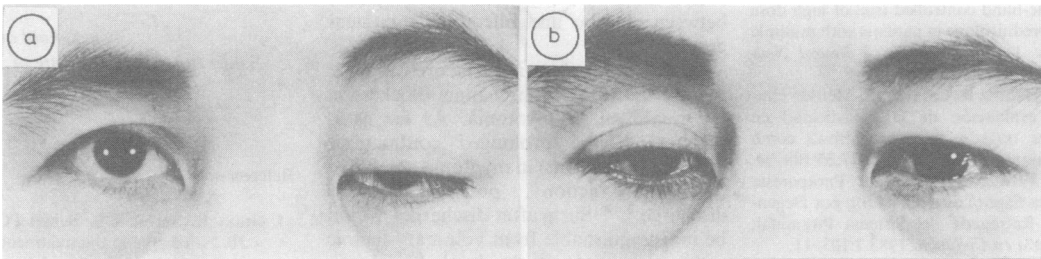


Fig The position of eyelids of patient 1 before (A) and after (B) the edrophonium injection.