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Visual evoked responses in diabetes

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SUMMARY It is commonly believed that diabetic optic neuropathy is very rare and visual loss in diabetes usually is attributed to other causes. We studied the extent of optic nerve involvement in 16 diabetics with no retinopathy or ocular disease and having an almost normal visual acuity, using visual evoked responses produced by pattern reversal stimulation. Comparing the responses with a group of 35 healthy subjects, the latency was increased by more than one standard deviation in 13 diabetics (81%) and by more than three standard deviations in 10 diabetics (62·5%), often associated with marked reduction in amplitude. There was good correlation between conduction in the optic nerve and peripheral sensory nerve. No correlation was noted to occur with duration of diabetes or diabetic control except perhaps with juvenile onset diabetes. Normal visual acuity was noted in many cases with severely slowed conduction showing early subclinical affection of optic nerves in diabetes. The extent of central nervous system involvement in diabetes has only recently been realised because of lack of physiological techniques and study of optic nerves in diabetes has not been attempted so far. The high incidence of abnormality of visual evoked potentials in diabetes could invalidate the usefulness of this test in diagnosing multiple sclerosis.

Lesions of the visual pathway have been studied for sometime using visually evoked responses, but it was more recently, after the introduction of the pattern evoked response that this method became acceptable as a sensitive and substantial tool to the clinician. It has been used widely to study demyelination in optic nerves in multiple sclerosis and is an early test for diagnosis.[1]

Diabetic affection of peripheral nerves is well known, but central neuropathy in diabetes has been appreciated only recently.[2] We have investigated visual evoked responses in diabetics. The latency to the major positive component of the pattern reversal response is relatively constant for a normal population.[3] The presence of a delay of this major positive wave indicates optic nerve pathology, provided local ocular abnormality like glaucoma and lesions of the vitreous lens, anterior chamber or cornea are excluded by clinical examination.[4] Macular splitting hemianopsia due to lesions of the optic tract or radiation do not affect the latency when the subject is fixing on the centre of the screen with the response recorded from a midline electrode.[4] Peak latency is unaffected by age up to 60 years,[3 4]. The upper limit of normal latency[5] is defined as the mean +3 SD and latency difference between the 2 eyes as 7 ms.[5] The amplitude of the VER is more variable than its latency and it is difficult to establish abnormality unless it is reduced to less than 2 μV or there is a marked difference between the two sides.[3 4] Abnormalities of waveform are useful, but difficult to quantitate.

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Methods

We studied visual evoked responses in 16 cases of diabetes and in 35 normal subjects. We used pattern reversal stimulation with a television display of black and white checker board pattern. The pattern was generated by brightness modulation on the face of a cathode ray tube. The square size generated was 4 cm each side and the brightness was kept constant. The distance of the television screen was kept fixed at 227·5 cm from the patient's eye, so that each check subtended a visual angle of 1° and the whole stimulating field subtended 10° at the eye. The reversal rate of the checker board pattern was 2 Hz. The subject lay on a couch, with the head inclined at 30° to the horizontal,

and was asked to fix on a square at the centre of the television screen. Each eye was occluded alternatively for the study. The site of electrode placement was similar to that described by Asselman *et al.*[4] The active recording electrode was a small unipolar Grass needle located in the midline 2 cm above the inion, subcutaneously. The indifferent subcutaneous needle was placed at the vertex. The ground electrode was on the forearm.

Analysis time was 300 ms and sweep velocity was 50 ms/cm. Low and high frequency filter setting was 1·6 Hz and 3·2 KHz respectively. The amplifier gain setting was 10 or 20 μv/cm. An average of 256 runs was taken and each run was checked for reproducibility by a 2nd run stored in a different memory bank.

For each eye the first prominent positive (downward deflection) peak called P_{100} and subsequent upward peak called N_{145} were studied. The latencies to the peak P_{100} and amplitude P_{100}–N_{145} were directly measured. We also studied the small negative (N_{75}) and a small positive wave preceding P_{100} and the latency between peaks in ascertaining the configuration of the waveform.

Sixty-one eyes were studied in the 35 normal healthy subjects whose age ranged from 19–50 years. There were 27 males and eight females. All had blood sugar and urea estimation. None had a significant alcoholic or smoking history.

The 16 diabetics taken into the study were healthy and were actively employed. There were 10 males and six females. They had no obvious nephropathy but had minimal clinical neuropathy in six cases (as shown by diminished or loss of ankle jerk or minimal peripheral sensory loss). Their age ranged from 16–60 years except one who was 71 years old. Duration of diabetes was from 3–27 years. They had normal vision of 6/6 in 10 cases, and 6/9 in four cases. In two cases the more affected eye had 6/18 vision. None had cataract, glaucoma, vitreous disease or retinopathy on clinical examination. All cases had visual fields and colour vision tested and had appropriate blood sugar estimation and serum B_{12} done. All these diabetics also had estimation of the sensory conduction of median nerve across the wrist, median motor conduction and somatosensory evoked potentials of the median and posterior tibial nerves recording with needle electrodes from the scalp.

Results

NORMAL SUBJECTS

The response to pattern stimulation in the normal subjects was a triphasic response with a prominent positive wave, P_{100} (Fig 1) with a peak latency of 86·0–103·0 ms (mean 95·8 ms ± 1 SD 4·37 ms). The major positive wave (P_{100}) was a downward peak in the record when either eye was stimulated. The mean peak amplitude was 6·6 μv with SD ± 2·3 μv. There was also a minor positive wave preceding P_{100} in most of the normal subjects.

DIABETICS SUBJECTS (fig 2)

The latency of the major positive component exceeded the mean latency of the control group by more than one standard deviation in one or both eyes in 13 of the 16 diabetics (81%). It was delayed by more than 3 SD in 10 cases (62·5%), this being bilateral in three cases. The delay was between 2–3 SD in one case and 1–2 SD in two cases. The maximum latency was 152 ms (fig 3). Marked latency difference between the two eyes (more than 7 ms) occurred in five patients in the severely delayed group (>3 SD). Of these cases, two had unilateral delay. Figure 4 shows a case with markedly delayed

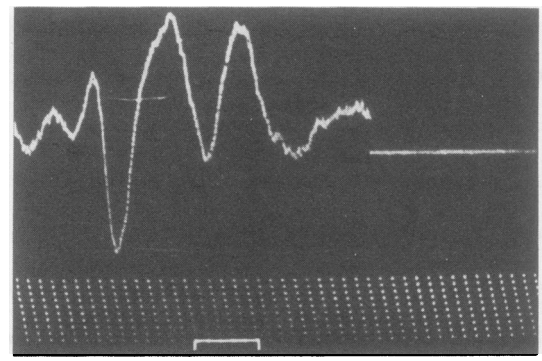

Fig 1 *Shows a normal triphasic response of the visual evoked potential to pattern reversal stimulation. Latency to P_{100} is 86·3 ms 50 ms/Division 2·5 μv/division*

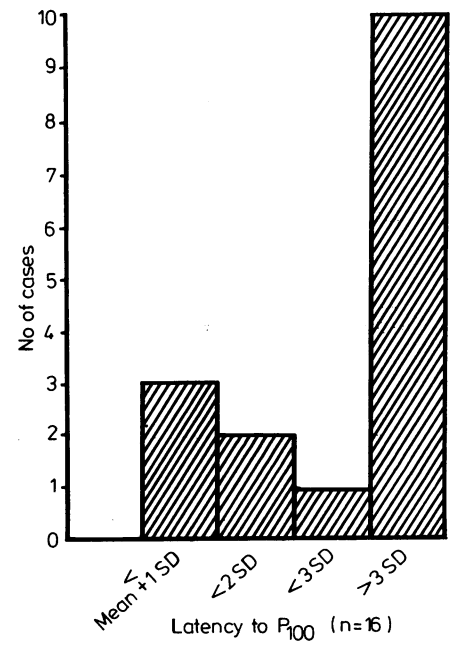

Fig 2 *Shows the delay in latency to P_{100} in the 16 diabetics in relation to the normal mean value.*

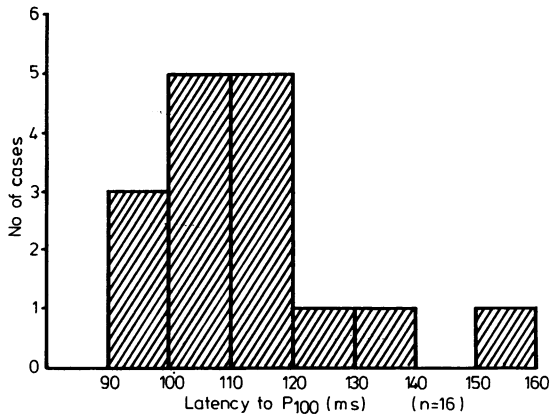

Fig 3 *Latency to P_{100} in ms in the 16 diabetics.*

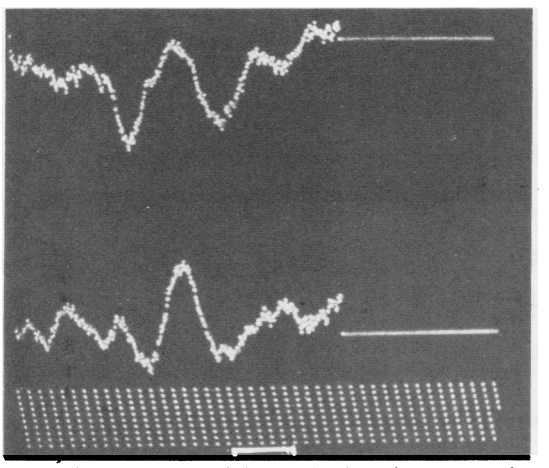

Fig 4 *Shows a case with bilateral delay of VER. P_{100} for right eye (lower tracing) is 126·0 ms. (visual acuity 6/9). P_{100} for left eye is 108·8 ms (visual acuity in 6/6). 50 ms/division. 2·5 μv/division.*

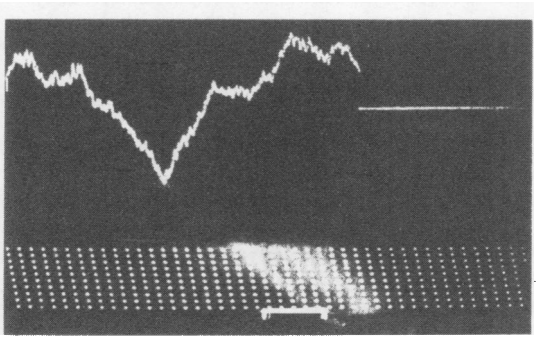

Fig 5 *Shows a broad and delayed VER. P_{100} for right eye is 135·3 ms (visual acuity 6/6) 50 ms/division. 2·5 μv/division.*

VER in both eyes and fig 5 shows a case with unilateral delay.

Amplitude less than 2 μv occurred in five cases in the severely delayed group and also in two cases with normal delay. When latency and amplitude were considered together, 15 diabetics were abnormal. Abnormally broad and delayed wave form occurred in five cases in the severely delayed group (fig 5).

No correlation of delayed conduction occurred with control of diabetes, except in juvenile onset diabetes. In the three juvenile onset diabetics, two had satisfactory control and these had normal value to P_{100}. They were diabetics for 10 years and 3 years respectively. The other juvenile onset diabetic of 3 years' duration who was very poorly controlled on insulin and having several admissions for ketotic coma had very prolonged latency of more than 3 SD of mean. Their latency difference was 11·9 msec and amplitude was less than 2 μv and they had abnormally broad wave form. No correlation occurred with duration of diabetes or the type of treatment.

Somatosensory evoked potential of the median and posterior tibial nerves recorded from the scalp could not be correlated to delay of P_{100}. Delay in sensory conduction in the median nerve across wrist correlated with delay of the visual evoked potential. (fig 6) All 11 cases with severely and moderately delayed visual evoked potentials (more than 2 SD of mean) had delay of median sensory conduction across the wrist. In cases with visual latency less than 2 SD of mean, only three out of five (60%) had sensory conduction delay in the median nerve.

No correlation occurred between VER latency and visual acuity. Most cases with visual evoked delay more than mean + 3 SD had a visual acuity of 6/9 or better.

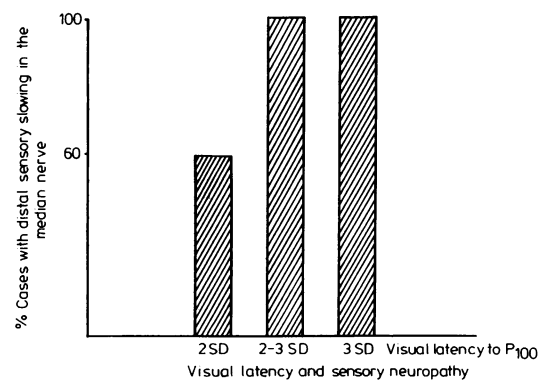

Fig 6 *Relationship between visual latency and median sensory conduction delay across the wrist in the diabetics.*

Discussion

Delay of the latency to the major positive wave P_{100} in the VER is a very sensitive method of detecting demyelination in the optic nerve.[1 4] Such demyelination causing delay in conduction is known to occur in optic neuritis and multiple sclerosis, but also may be seen in ischaemic optic neuropathy, optic nerve compression and spinocerebellar degeneration.[3 4]

Our diabetic patients did not have any complaints referable to the eye and their visual acuity was near normal. Yet an appreciable delay of conduction in the optic nerve occurred in 62·5%. The delay was unilateral suggesting optic nerve affection. In some, the delay was bilateral suggesting diffused affection of the visual pathway. Even though there were no symptoms suggestive of optic neuritis or optic disc appearance suggestive of optic neuritis or atrophy in diabetes, the incidence of demyelination of the optic nerve seems to be similar to that in multiple sclerosis where signs and symptoms of optic neuritis or optic atrophy usually are obvious.[4 5]

Central neuropathy in diabetes was not appreciated until recently. De Jong[2] described clinical and pathological evidence for a diabetic myelopathy and encephalopathy. Changes in the optic nerves occurred as frequently as in the peripheral nerves in diabetics in our study, yet none of these cases had clinical evidence of optic neuritis and their visual acuity was normal. Conduction in optic nerve parallel peripheral nerve conduction, but not the spinal somatosensory conduction. The absence of correlation between the latter and peripheral nerve involvement has been noted before.[6] Diabetes as a cause of optic neuritis is very rarely mentioned amongst ophthalmologists. Some have even doubted the existence of such an entity.[7 8] However, Reske-Nielsen and others,[9] in longstanding juvenile diabetics, reported severe demyelination and degeneration of axis cylinders in the optic chiasma and associated severe demyelination of other cranial nerves. Such cranial neuropathy was present in cases with or without symptoms.

Subclinical sensory neuropathy occurs early in diabetes,[10 11] and is due to segmental demyelination which is the main finding in diabetic neuropathy.[11 12] Subclinical neuropathy, which occurs in as many as 40–73% of cases of diabetes,[6 10 11] could very well affect the optic pathway. Demyelination leads to either conduction block if the lesion is large or slowed conduction if lesion is small. Demyelinated fibres cannot conduct trains of impulses at physiological frequency, resulting in a block.[13] The delay in VER in our diabetics is as much as 55 ms which is of the order occurring in multiple sclerosis. Such prolonged delay cannot be explained on the basis of slowing of saltatory conduction alone. Increased synaptic delay at retinal, geniculate and cortical levels could occur, but cannot contribute much to the delay of VER.[13 14] The electroretinogram is usually normal in optic nerve demyelination.[15] McDonald[13] explains this delay on the basis of slow continuous conduction occurring in the demyelinated optic nerve.

Pattern reversal evoked responses study has been of particular value in the early diagnosis of multiple sclerosis when the patient presents evidence of some lesion outside the visual system, for example a spastic paraparesis.[4] This test in multiple sclerosis could be invalidated if there is associated diabetes, even if it is of a mild degree.

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