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Central Conduction Time in Childhood Autism

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To investigate the integrity of the brain-stem in 20 mentally handicapped children who met the Rutter criteria for autism, brain-stem auditory evoked potentials were obtained for a range of stimulus intensities. Central conduction times (CCTs) were calculated for the Wave I–Wave V interval of the brain-stem potentials. In children under 14 years of age CCTs were normal. In children 14 years of age and over, three of four girls and eight of nine boys had CCTs exceeding normal limits when compared with a group of controls of normal intelligence, matched for age and sex. CCTs recorded from a group of non-autistic mentally handicapped children were within normal limits. The age distributions are consistent with a maturational defect in myelination within the brain-stem in autism, a defect which may have a much wider anatomical distribution throughout cortical and subcortical structures.

Childhood autism was delineated almost five decades ago by Kanner (1943); the central feature is the presence of severe and unique distortions of social interaction and communication. Most children presenting with the syndrome are severely mentally handicapped. Wing (1981) has suggested that autistic children may be part of a larger group, characterised by the triad of impaired social interaction, impaired communications, and impaired imagination. While the precise aetiology of the condition remains unknown, there is now general agreement that the underlying basis of the disorder resides in either brain damage or impaired brain development (Prior, 1987). A number of brain areas have been implicated, including the frontal lobe, the limbic system, and the dorsal midbrain (Ploog, 1979; Wing, 1981).

In a review of the functional neuroanatomy of infantile autism, Ornitz (1983) considered that the symptoms can best be explained in terms of dysfunction of brain-stem and related diencephalic systems. Evoked potentials can be used to evaluate the functional integrity of the brain-stem. Major advantages of the procedure are the non-invasiveness of the technique and the objective nature of the test. Several studies have reported abnormalities in the brain-stem auditory evoked potentials (BAEP) in autistic children, the most consistent being delayed conduction time (Sohmer & Student, 1978; Novick *et al*, 1980; Rosenblum *et al*, 1980; Skoff *et al*, 1980; Tanguay & Edwards, 1982; Taylor *et al*, 1982). Nevertheless, other investigators have failed to confirm this abnormality (Rumsey *et al*, 1984; Courchesne *et al*, 1985). The findings of Courchesne *et al* (1985) are particularly interesting in that the study was conducted in a group of autistic individuals without mental handicap. Important sources for the differences in findings reside in the variability of evoked potentials and the choice of controls (Prior, 1987). For example, throughout childhood significant changes occur in the brain-stem potentials with age, and the abnormal responses from girls appear significantly earlier than from boys (McClelland & McCrea, 1977; Houston & McClelland, 1985).

Childhood autism may not be a single disorder but may arise from any of several specific brain lesions, dysfunctions, or developmental defects. In particular, it is possible that autism in mentally handicapped children may have quite different origins from that in children of average or above average intelligence (Bartak & Rutter, 1976). Given that the syndrome is much more common among severely mentally handicapped children, the question remains as to the significance of the reported abnormal brain-stem findings in mentally impaired autistic children.

The present study was undertaken to investigate further the evidence for brain-stem conduction delay in mentally handicapped children and also to examine the relationship between brain-stem function, cognitive function, and behaviour. Particular attention was paid to the possible effects of age, sex, and intelligence on response variability.

Method

A major effort was made to identify all autistic mentally handicapped children within the Northern Ireland Eastern Health and Social Services Board (population 636 000). Most of the patients in the study were identified through a register of children attending schools for children with a mental handicap within the area. A survey was made of all children attending 'special care' schools and units to identify any with autistic features. In addition, professionals working with handicapped children were asked to identify any other children with autistic features not known to the authors or not on the register. Detailed physical examinations were made to exclude major metabolic and neurological disease and serious sensory impairments. Fourteen boys

and six girls were identified, all satisfying the Rutter diagnostic criteria for childhood autism (Rutter, 1978*a*).

A detailed assessment of each child was made by one of the authors (DGE) trained in the use of the Schedule of Children's Handicaps, Behaviour and Skills (Wing & Gould, 1978). The schedule consists of 130 items, embracing the following categories of behaviour: motor skills; educational attainment; mobility; initiative and persistence; domestic skills; play; self-care; social interactions; independence; behaviour problems; communication; repetitive routines and resistance to change; abnormal responses to sound or visual stimuli; abnormal responses to peripheral stimulation; abnormal bodily movements.

Observations of each child were complemented by a detailed interview with an informant. In the case of community patients this was usually the mother, and in the case of in-patients this was a nurse who had known the patient for at least the previous year and had cared for the patient in the month before the assessment. The schedule was used to establish behavioural profiles on each child for the three behavioural components of the Rutter criteria – impaired social development, delayed and deviant language development, insistence on sameness. The schedule also permitted the derivation of the Vineland social age and social quotient (SQ). The mean (s.d.) Vineland SQ for the group was 28 (20).

Two separate control groups were identified for neurophysiological investigation. One group comprised 54 children of normal intelligence, a subgroup of whom were matched for age and sex. The other was a group of mentally handicapped non-autistic children (8 boys, 4 girls) matched for age and sex (mean Vineland SQ 23 (19)).

Brain-stem auditory evoked potentials

All residential children were investigated in hospital and the remaining community subjects were studied at the Research Laboratory of the Department of Mental Health. Recordings were made using a portable evoked response system based on the Apple II microprocessor (McAllister *et al*, 1983). Simultaneous bipolar recordings were made from vertex and right and left mastoid processes. Auditory stimuli consisted of pulses of 100 μs each, presented at a rate of 10 per second and delivered through a 'TDH 39' headphone. Each ear was investigated separately and recordings were made for a range of stimulus intensities from 70 dB nHL (normal hearing level) to threshold. Averages of at least 2048 individual responses were formed at each intensity. Plots of each coherent average consisted of pre- and post-stimulus intervals both of 12.5 ms (Fig. 1).

The combined plots of pre-stimulus and post-stimulus intervals provided estimates of the signal-to-noise ratio and indicated the confidence which could be attached to the measurement made on individual response components. Two additional procedures were adopted to maximise the accuracy of measurements. The first consisted of digital filtering (zero phase shift) of the wide-band responses with a band width of 200–1500 Hz. Secondly, response latencies were measured on the microprocessor screen using a cursor, which provided a more accurate and reliable measure than conventional methods (time resolution 0.1 ms).

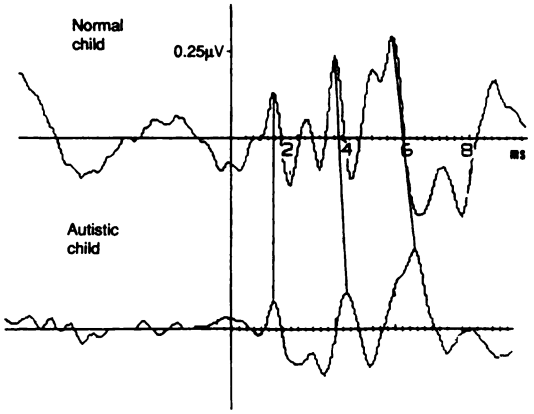

Fig. 1 Typical BAEPs to 70 dB nHL unilateral clicks in the present study. Waves I, III and V (joined by vertical lines) show increased latencies in the autistic child. The plots for both ears for each child have been combined.

The restlessness of many children when awake prevented reliable identification of wave components and accurate estimates of auditory threshold. For these children repeat recordings were carried out under light general anaesthesia using enflurane. Possible effects of enflurane anaesthesia on the evoked potentials were investigated in five children who required anaesthesia to establish auditory thresholds. A mean (s.d.) latency increase of 0.02 ms (0.11) with enflurane was observed, which is within the experimental error of the method.

The thresholds of the BAEPs recorded for each ear provided an objective measure of auditory threshold. The interval between wave I, which arises from the auditory nerve, and waves III and V, which arise from the lateral lemniscus and inferior caliculus respectively, provided measures of central conduction time (CCT).

Results

In two children with an estimated hearing level of 30–40 dB, mild bilateral hearing loss was diagnosed. These two children were included in all subsequent observations. In all other children auditory thresholds were within the normal range.

The frequency distribution of brain-stem CCTs (I–V interval) for the group of autistic children were first compared with the corresponding distribution for normal controls (Fig. 2). While the two distributions overlapped, a clear skewing was observed, with longer latencies found among autistic children ($P<0.001$).

The distribution of CCTs for the autistic group was re-examined according to age and compared with the age curve obtained for normal children. Figure 3, which plots the 95% and 5% confidence limits for normal children, shows the gradual shortening in mean CCT with age. This age change was absent in the plots of CCTs for autistic children: for younger autistic children, all CCTs were within

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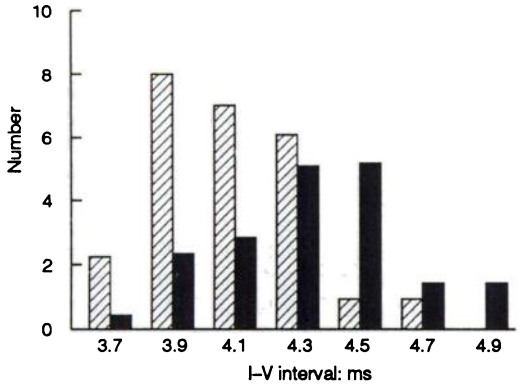

Fig. 2 The frequency distribution of the BAEP I–V interval (both ears) for the 20 autistic children (both ears) (■) and for 54 normal controls (one ear only) (▨).

Fig. 4 BAEP I–V intervals in autistic and control subjects 14 years and over showing means and standard errors. AUT, autistic (9 boys, 4 girls); MH, mentally handicapped non-autistic controls (8 boys, 4 girls); NC, normal controls (14 boys, 14 girls). The most prolonged ear value has been plotted for all subjects.

the confidence interval for normals, while several of the older children lay outside this latency interval.

When account was taken of the sex differences in the BAEPs, greater differentiation between normal and autistic children was obtained. Among children under 14 years of age no differences were observed in the CCTs of the two groups. By contrast, for autistic children 14 years and over, eight of the nine boys and three of the four girls exceeded the upper limit of normal ($P<0.01$) (Fig. 4). No significant inter-aural differences were evident in the CCTs for either patients or controls. Although less marked, the same pattern was observed for the I–III and III–V intervals, that is, an age-dependent trend was observed for longer intervals among the autistic group. No differences were observed between the CCTs of non-autistic mentally handicapped children and children of normal intelligence (Fig. 4).

The relationship between CCT and individual items on the handicap schedule was then examined for the group of autistic children. The Vineland SQs for autistic children with abnormal CCTs were significantly lower (mean 17.4) than those with normal CCTs (mean 37.8) ($P<0.003$). While significantly more children with normal CCTs had deviant language, this difference was entirely attributable to the virtual absence of language among those children with abnormal CCTs. Spinning behaviour was also more common among those children with normal CCTs. No other significant differences were found.

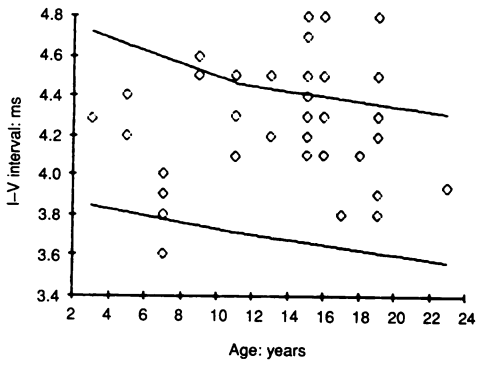

Fig. 3 Age distribution of the I–V interval (both ears) for the 20 autistic children (six are double plots) together with the 5% and 95% limits drawn for 54 normal children.

Discussion

One observation in the present study which at first sight appears discrepant with the age of onset of the disorder is the emergence of prolonged CCTs in older autistic children. While this might suggest the late onset of new pathology, it is also quite consistent with a developmental defect in myelination. Normal children show a progressive shortening in the brain-stem I–V interval attributable to the normal myelination process (Houston & McClelland, 1985). This pattern was absent in the autistic group. A perinatal insult such as hypoxia could interfere with myelination and account for the absence of the normal developmental decrease in CCT. Such a myelination defect may also account for the late occurrence of epilepsy in children with autism through a relative deficiency of ascending inhibitory input to the cortex leading to excessive neuronal excitability.

The study provided an opportunity to examine the relationship between abnormal function of the brain-stem and specific behaviour. The Vineland SQs of autistic children with abnormal CCTs were significantly lower than those with normal CCTs; while this might simply be a reflection of non-specific brain damage, it was not a feature of severely mentally handicapped non-autistic children. Several abnormal types of behaviour were more common

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among autistic children with normal CCTs. While these were mostly in the area of language deviance, few of the group with abnormal evoked potentials had sufficient language to assess for the presence of deviance. The study failed to support the observation of Fein *et al* (1981), who reported higher frequencies of aloofness, resistance, and object preoccupation among children with abnormal brain-stem potentials.

As Rutter (1978*b*) has commented, the term 'autism' was not introduced by Kanner merely as a descriptive label, but in order to identify a syndrome underlying which one might hope to isolate a specific disease or diseases, each with their own aetiology. The validity of the syndrome, characterised by the three core symptoms of language retardation, ritualistic or compulsive phenomena, and a general failure to develop social relationships, has stood the test of rigorous evaluation over many years. Identification of the underlying disease processes, however, has been less successful. In any investigation of childhood autism in which comparisons are being made between autistic and non-autistic children, it is essential to control for other important variables. In the present study of CCT, three such variables have been considered: age, sex, and intelligence.

Of the many and controversial investigations of evoked potentials in childhood autism, that by Courchesne *et al* (1985) is the first to take specific account of intelligence. In their study of non-mentally handicapped autistic individuals, evoked brain-stem potentials were within normal limits. In non-mentally handicapped children, therefore, disorder within the brain-stem auditory pathway would not appear to be an essential prerequisite for autism.

However, the prevalence of the autism syndrome varies dramatically with level of intelligence. In one of the few epidemiological studies, Wing (1981) found that among children with IQs higher than 70 only 0.01% had the characteristic triad of impaired communication, social interaction, and imagination. This increased systematically to 2% of children in the IQ range 50–79, to 50% of children in the IQ range 20–49, and to 80% in the IQ range 0–19. Nevertheless, autistic features could not be attributed to mental handicap *per se*, as many severely retarded children were quite sociable and without autistic features.

The syndrome probably does not have a single aetiology but emerges from many different pathophysiological processes. The occurrence of autism in profoundly mentally handicapped children may have quite different origins from that arising in less handicapped children of average and above average intelligence. In support of such a view is the evidence of a poorer prognosis and higher prevalence of epilepsy among severely mentally handicapped autistic children compared with autistic children of normal intelligence (Bartak & Rutter, 1976).

Several lines of inquiry have suggested impairments of function in the midbrain and brain-stem. Ornitz (1978) has suggested the brain-stem vestibular system, Rimland (1964) the reticular formation, MacCulloch & Williams (1971) the dorsal brain-stem, and a number of studies have reported abnormalities of the brain-stem auditory pathway. The proposal by Courchesne *et al* (1985) seeks to reconcile the divergent evidence of normal CCT in autistic children of normal intelligence and delayed CCT in severely mentally handicapped autistic children. The critical pathology may be in the extralemniscal brain-stem pathway subserving both auditory and alerting functions. Small restricted lesions in the central nervous system of children of normal intelligence may spare the main auditory pathway while interfering with general alerting responses, including cortical responses to auditory stimuli. More extensive lesions involving the primary auditory pathway within the brain-stem will result in delays in CCT. This extension of pathology may also account for the severe intellectual retardation found in this group.

Uncertainty remains regarding any single psychological deficit underpinning the autistic triad. Nevertheless, the importance of language has been recognised not only for communication but also for making sense of the environment. If a deficit in language is a major or indeed a primary one, then developmental abnormalities at any point within the central auditory pathway leading to impairments in auditory perception may be of considerable aetiological importance. The present study provides strong support for such an abnormality in mentally handicapped autistic children. While auditory brain-stem function would appear to be normal in non-mentally handicapped autistic children, functional abnormalities within higher-level auditory pathways have been observed (Courchesne *et al*, 1985).

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