

# UC San Diego

## UC San Diego Previously Published Works

### Title

Abnormal Neuroanatomy in a Nonretarded Person With Autism: Unusual Findings With Magnetic Resonance Imaging

### Permalink

<https://escholarship.org/uc/item/9c89759b>

### Journal

JAMA Neurology, 44(3)

### ISSN

2168-6149

### Authors

Courchesne, Eric  
Hesselink, John R  
Jernigan, Terry L  
et al.

### Publication Date

1987-03-01

### DOI

10.1001/archneur.1987.00520150073028

Peer reviewed

11. Walker AE: Dilation of the vertebral canal associated with congenital anomalies of the spinal cord. *AJR* 1944;52:571-582.

12. Gunderson CH, Solitare GB: Mirror movements in patients with the Klippel-Feil syndrome. *Arch Neurol* 1968;18:675-679.

13. Mackenzie NG, Emery JL: Deformities of the cervical cord children with neurospinal dysraphisms. *Dev Med Child Neurol* 1971;13(suppl 25):58-67.

14. Giordano GB, Davidovits P, Cerisoli M, et al: Cervical diplomyelia revealed by computed tomography (CT). *Neuropediatrics* 1982;13:93-94.

15. Naidich TP, McLone DG, Fulling KH: The Chiari II malformation: IV. The hindbrain deformity. *Neuroradiology* 1983;25:179-197.

16. Whittle IR, Besser M: Congenital neural

abnormalities presenting with mirror movements in a patient with Klippel-Feil syndrome: Case report. *J Neurosurg* 1983;59:891-894.

17. Levine RS, Geremia GK, McNeill TW: CT demonstration of cervical diastematomyelia. *J Comput Assist Tomogr* 1985;9:592-594.

18. Herren RY, Edwards JE: Diplomyelia (duplication of the spinal cord). *Arch Pathol Lab Med* 1940;30:1203-1214.

19. Emery JL, Lender RG: The cord lesion in neurospinal dysraphism (meningomyelocele). *J Pathol* 1973;110:83-96.

20. James JCC, Lassaman LP: Diastematomyelia: A critical review of 24 cases submitted to laminectomy. *Arch Dis Child* 1964;39:125-130.

21. Reynolds AF: Cervical diastematomyelia. *Neurosurgery* 1985;17:1014.

22. Bently JFR, Smith JR: Developmental pos-

terior enteric remnants and spinal malformations: The splint notocord syndrome. *Arch Dis Child* 1960;35:76-86.

23. Matson DD, Woods RP, Campbell JB, et al: Diastematomyelia (congenital clefts of the spinal cord): Diagnosis and surgical treatment. *Pediatrics* 1950;6:98-112.

24. Paget DH: Neuroschisis and human embryonic maldevelopment: New evidence on anencephaly, spina bifida and diverse mammalian defects. *J Neuropathol Exp Neurol* 1970;29:192-216.

25. Thompson JS, Thompson M: Patterns of transmission of single gene traits, in Thompson JS, Thompson M (eds): *Genetics in Medicine*. Philadelphia, WB Saunders Co, 1980, p 78.

## Abnormal Neuroanatomy in a Nonretarded Person With Autism

### Unusual Findings With Magnetic Resonance Imaging

Eric Courchesne, PhD; John R. Hesselink, MD; Terry L. Jernigan, PhD; Rachel Yeung-Courchesne

● Recent studies of infantile autism using computed tomographic scanning emphasized the importance of studying cases of classic autism (Kanner's syndrome) without complicating conditions such as mental retardation. Computed tomographic scan studies of such patients reported no evidence of anatomical abnormalities of cerebral hemispheres or of subcortical structures, which are defined by landmarks such as the lateral ventricles and lentiform nuclei. Examination of the cerebellum was not mentioned. The most recent postmortem neuropathologic study reported significant cerebellar abnormality, but the study was of a severely retarded autistic individual. Using magnetic resonance imaging, we have found in vivo evidence of a significant and unusual cerebellar malformation in a person with the classic form of autism uncomplicated by mental retardation (current nonverbal IQ = 112), epilepsy, history of drug use, postnatal trauma, or disease. The finding showed hypoplasia of the declive, folium, and tuber in posterior vermis, but not of the anterior vermis, and hypoplasia of only the medial aspect of each cerebellar hemisphere. The right posterior cerebral hemisphere also showed pathologic findings. (*Arch Neurol* 1987;44:335-341)

Infantile autism is a neural disorder that severely affects social, language, and cognitive development.<sup>1-4</sup> The etiology of infantile autism is unknown. The neuroanatomical substrates associated with this disorder have not been firmly established. While there have been computed tomographic (CT) scan reports that subgroups of autistic persons have anomalous cerebral asymmetries (right parieto-occipital regions wider than left<sup>5</sup>) or abnormalities of the ventricular system,<sup>6,7</sup> there have also been reports that these structures are clinically normal in most autistic persons<sup>8</sup> or are similar in autistic and matched control groups.<sup>9</sup> It has been argued that mental retardation has been a complicating factor in some CT scan studies and that CT abnormalities could just as well be related to mental retardation as they are to autism.<sup>10</sup>

Recently, therefore, emphasis has been placed on the importance of studying patients with classic autism (Kanner's syndrome) uncomplicated by concurrent conditions such as mental retardation.<sup>3,11-14</sup> According to this view, to determine which conditions must be present for autism to develop

or which conditions are associated specifically with autism, it is necessary to study individuals who do not have concurrent conditions that may significantly contribute to observed abnormalities above and beyond those due to autism alone.

Computed tomographic scan studies of such classic cases of autism have found no evidence of anatomical abnormalities of cerebral hemispheres or of subcortical structures that are defined by landmarks such as the lateral ventricles and lentiform nuclei.<sup>10,15</sup>

Examination of the cerebellum has not been mentioned in the CT scan reports on classic cases of autism, and, in fact, there are no in vivo or postmortem reports examining the cerebellum in such classic cases. However, with regard to *retarded* autistic cases, significant pathologic features of the cerebellum were found in five of a total of eight cases in three reports.<sup>16-18</sup> All eight individuals studied were severely retarded, and had a wide variety of complicating disorders and traumas, including phenylketonuria, severe concussions, and epilepsy. In one of these reports, Bauman and Kemper<sup>18</sup> found, in the postmortem study of a severely retarded man, marked Purkinje cell loss in the neocerebellum, as well as cell loss in several deep cerebellar nuclei—fastigial, globose, and emboliform. In a second report,<sup>17</sup> CT scans of all three severely retarded "autistic" children

Accepted for publication Nov 10, 1986.

From the Neuropsychology Research Laboratory, Children's Hospital Research Center, San Diego (Dr Courchesne and Mrs Yeung-Courchesne); the Departments of Neurosciences (Dr Courchesne), Radiology (Drs Hesselink and Jernigan), and Psychiatry (Dr Jernigan), University of California at San Diego School of Medicine, La

Jolla; and the Psychiatry Department, Veterans Administration Medical Center, San Diego (Dr Jernigan).

Reprint requests to Neuropsychology Research Laboratory, Children's Hospital Research Center, 8001 Frost St, San Diego, CA 92123 (Dr Courchesne).

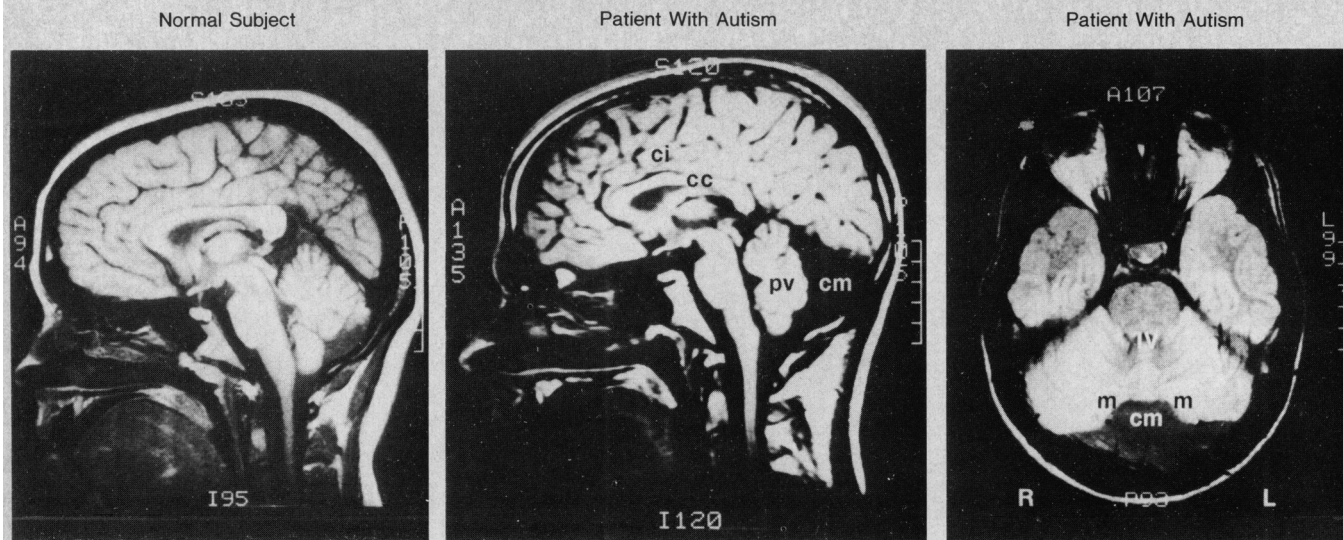


Fig 1.—Magnetic resonance images of midline sagittal section in normal subject (left) and midline sagittal (center) and axial (right; 7.5 mm above fourth ventricle) sections in nonretarded patient with infantile autism. In latter, hypoplasia of superior posterior vermis (pv), which includes declive, folium, and tuber, and of medial aspect of cerebellar hemispheres (m) is evident. Folia of pv are incompletely formed. Cisterna magna (cm) is enlarged. Other midline structures, including fourth ventricle (IV), brain stem, diencephalon, corpus callosum (cc), and medial cortical areas (eg, cingulate gyrus [ci]), appear normal.

studied showed hypoplasia of the cerebellum, especially in the vermal portion. The three children ranged in age from 20 to 44 months, and their intellectual developmental level ranged from 2 to 6 months. In a third report of individuals with autisticlike behavior,<sup>16</sup> marked Purkinje cell loss was reported in one of four cases studied. Of the three cases for whom there was no report of cerebellar pathology, one showed evidence of phenylketonuria. Another suffered a cerebral concussion during the fourth year of life and showed no learning for almost 18 months thereafter, but he did develop bonds of attachment with his mother. The third was a girl who showed normal development during the first 18 months and then a progressive degeneration of function, including hand wringing, posturing of the upper extremities, and grimacing. The clinical picture of this third child is suggestive of Rett's syndrome.<sup>19</sup> In summary, then, cerebellar anatomical abnormalities have only been found in autistic persons with severe mental retardation and epilepsy—either of which may be correlated with cerebellar pathologic findings.

Currently, the brain imaging technology that yields the most anatomical detail is magnetic resonance imaging (MRI). In particular, MRI is much superior to CT technology in imaging the cerebellum and the periphery of the brain. In the present report, MRI was used to examine the cerebellum, cerebral cortex, and subcortical structures in a nonretarded, high-function-

ing person with autism but without complicating syndromes.

#### REPORT OF A CASE

A 21-year-old right-handed man meets the *Diagnostic and Statistical Manual of Mental Disorders, ed 3 (DSM-III)*, diagnostic criteria for autism. He does not have any other neurologic or psychiatric disorder and has no history of taking neurologic or psychiatric medications.

The patient's mother recalls an uneventful pregnancy, with the exception of a viral cold contracted during the end of the first trimester. The patient was born at full term without complications. He was the third child born to his parents. The patient's one younger and two older siblings are normal. Throughout infancy and childhood, the patient is reported to have been healthy, except for the usual occasional colds that were readily resolved by medication. His height and weight have been within normal limits from birth onward. The patient achieved motor developmental milestones on a normal schedule as follows: rolling over at 3 months of age, sitting independently at 6 to 7 months, crawling at 7 to 8 months, standing unsupported at 9 to 10 months, and walking independently at 15 months. The patient's father, a physician, reported that during infancy and childhood the patient's "fine motor coordination appeared normal, as judged by his excellent manual dexterity and his skill in gross motor activities (walking on narrow walls, tree climbing, bicycle riding, etc)."

The parents judged the infant to be healthy and bright; he cooed and his interactive play with parents during infancy was normal. However, both parents observed that the infant tended to be quieter than their two older children. He had not spoken any words by 12 months.

The patient's first words were *helicopter* and *cookie* at 18 months.

During his third and fourth years of life, the parents observed that he was socially isolated and that he was not initiating social contact or showing any evidence of social communication. He preferred to play alone in his room and would become extremely upset if he was interrupted during his repetitive play with objects. He had no playmates and would not ask questions or state his needs other than to hold someone's hand and use that person's hand to point at something. He still did not speak two-word phrases. He spent hours spinning tops and records and flushing the toilet to watch the spinning water.

Between the ages of 3 and 4 years, he received thorough neurologic examinations at two separate medical centers (one was The Johns Hopkins Medical Center, Baltimore); both concluded that there was no detectable neurologic abnormality. Electroencephalography at that time was normal. Medical examinations since then have continued to reveal no detectable neurologic syndromes. Brain-stem auditory evoked response audiometric testing at age 20 years was also normal (see reference 8 for details of testing procedure used).

After the age of 4 years, he was placed in special education and speech classes for autistic and aphasic children. From 8 years of age onward, he was also in a socialization therapy group for nonretarded autistic children.

By 6 years of age, he still did not say "I" or "me." At this time, he was placed in a "talking typewriter program." With this, he began to learn the alphabet and to read. He began to speak echolalically, first with words, then phrases. By the age of 13 years, he still had difficulty with mixing up the pronouns *I* and *you* and referred to himself in the third person. However, by this age,

the patient performed within normal limits on speech and language tests of syntax, semantics, morphology, and phonology. However, his comprehension and use of language remained peculiar and severely impaired. He spoke idiosyncratic phrases, such as saying "get pigged" for "get dressed." He referred to himself using several peculiar names, such as "Mole," "Pack," and "Alexander Wakefield Applegate." Whether alone in his room or with others in class, he often carried on loud conversations with himself; the other "person" in the conversation was "Panda," a stuffed bear he received as a young child. He once told a teacher, "I like talking to myself or Panda because that is grown-up talk. To me, talking to other people and saying words like *Hi* is toddler talk."

His scores on the Comprehension subtest of the Wechsler Intelligence Scales over a ten-year period (8 to 18 years of age) have averaged 2.5 SDs below normal. From age 8 to 9 years onward, he became a prolific writer of lists—lists of time, dates, holidays, and programs on television and radio. He became absorbed in memorizing maps and their lists of "places of interest." His long-term memory for details of subjects that interest him is somewhat above normal.

Currently, he works in a bicycle shop putting together new bicycles but does not know how to repair them. He is an avid bicycle rider and has been since early childhood. He continues to show little spontaneity, especially in social situations. He remains self-contained and socially isolated and is virtually indifferent about other autistic persons he has known for more than ten years through a weekly socialization therapy group. He knows many social rules that are appropriate for classrooms, churches, buses, and the like, but he follows the rules in an almost mechanical, rote fashion. He continues to be unaware of the social and personal needs of others, speaks with others as little as possible, and takes no initiative to make friends. He is, however, aware that he has a handicap called autism and that he differs from others, and he appears to feel badly about this.

Psychometric testing has been performed several times. Between 8 and 21 years of age, the patient received tests of nonverbal IQ, including the Leiter and the Performance subtests of the Wechsler Intelligence Scale for Children, Revised (WISC-R), and Wechsler Adult Intelligence Scale, Revised (WAIS-R). Results show nonverbal IQs of 113, 108, 121, and, most recently, 112. At the age of 4 years, his IQ was 63, as measured by the Stanford-Binet; this IQ principally reflects the patient's severe language impairment at that time. Between 8 and 21 years of age, there has been a steady increase in verbal ability. Results of the Verbal subtests of the Wechsler Intelligence Scales have been 72, 82, and, most recently, 96. His language quotient, based on the Test of Adolescent Language, is 89, which is in the low normal range. Recent tests of reading, spelling, and arithmetic with the Wide-Range Achievement Test (WRAT) reveal normal

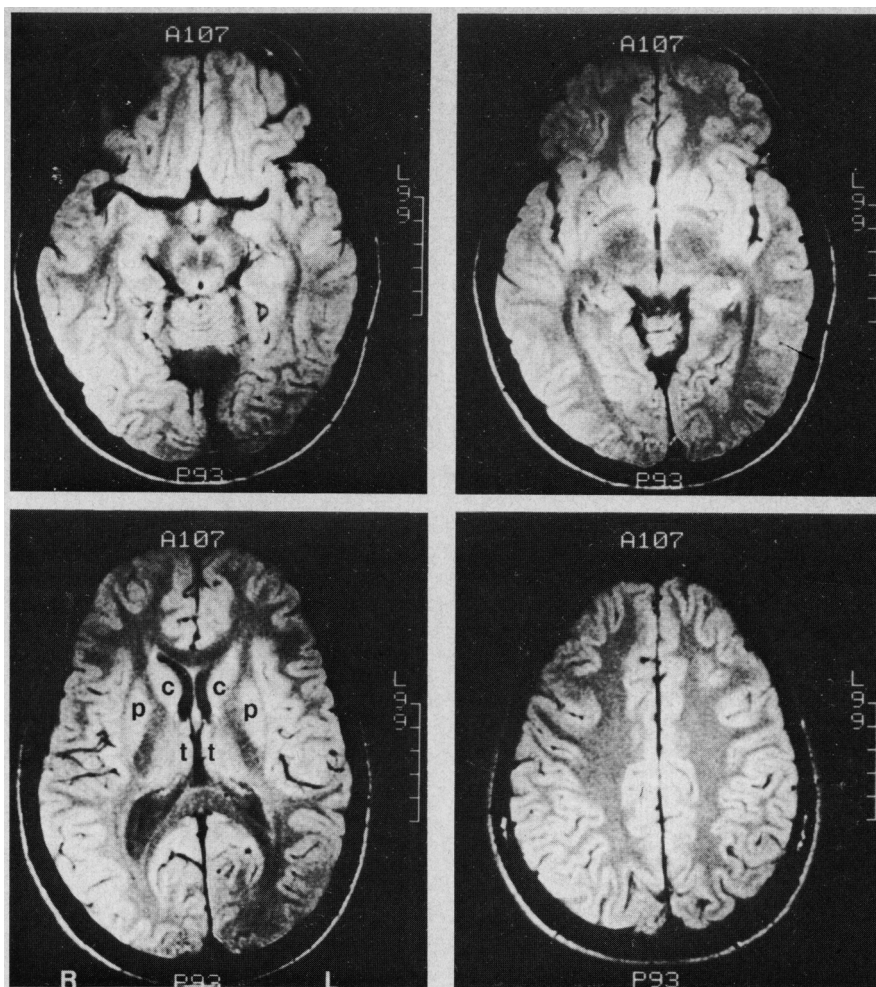


Fig 2.—Cortical and subcortical structures in axial sections at levels of midbrain (top left), third ventricle (top right), lateral ventricles (bottom left), and centrum semiovale (bottom right) in same nonretarded autistic patient as in Fig 1. c indicates caudate; p, putamen; and t, thalamus.

scores (100, 109, and 107, respectively). Nonetheless, recent tests also show his *speaking vocabulary* to be more than 1 SD below normal, although his speaking grammar and reading vocabulary are normal. The patient has normal performance on the Bender test of visual-motor ability and has an above-average Memory Quotient of 120 on the Wechsler Memory Scale.

The pattern of his scores on Wechsler Intelligence Scales has remained constant across six test sessions over a ten-year period since he was 8 years old; the nonverbal subtests Block Design and Object Assembly have been consistently between 2 and 3 SDs above the verbal subtests Vocabulary and Comprehension. This pattern of extreme disparity between these nonverbal and verbal subtests is similar to the pattern found by Rutter<sup>20</sup> and others (A. J. Lincoln, PhD, E. Courchesne, PhD, B. A. Kilman, et al, unpublished observations, 1986) in large samples of high-functioning, nonretarded autistic persons.

The quality of the patient's speech is distinctly dysprosodic. It is arrhythmic, clipped, and hesitant. His voice is typically monotonic, and any changes in tone and loudness are abrupt and inappropriately

placed. The tone of his voice has a tinny, hollow, and mechanical quality.

Recent examinations of motor function confirm that the patient does not have major or debilitating motor impairment; there is no evidence of hypotonia, and he has good dexterity and visual-motor coordination. He did, however, have significant difficulty keeping his balance when his eyes were closed, and, when asked to perform motor sequences that were new to him, he could not do so with the facility expected of normal functioning.

After obtaining informed consent from the patient and his parents, we conducted an MRI scan of this patient's brain. A 1.5-tesla whole-body imager (Signa) was used. Three multisection sequences were performed: (1) a multisection spin-echo sequence (TR-2000, TE-25, 70 ms) in the axial plane from the foramen magnum to vertex; (2) a multisection spin-echo sequence (TR-2000, TE-25, 70 ms) in the coronal plane through the brain; and (3) a multisection T1-weighted sequence (TR-600, TE-25) in the sagittal plane near the midline. Sections were 5 mm in thickness, and there were 2.5-mm gaps between adjacent sections.

As seen in Fig 1, specific regions in the

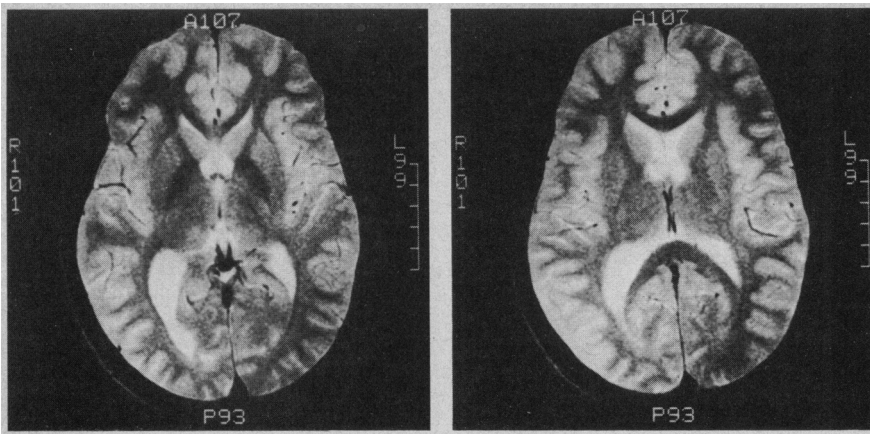


Fig 3.—Views at two axial levels (right axial section is 7.5 mm superior to left axial section) of same autistic patient as in Fig 1 show sulcal widening in right posterior hemisphere and abnormally enlarged posterior horn of lateral ventricle in right hemisphere. R101 indicates right side; L99, left side.

vermis and medial neocerebellar hemispheres of our patient are abnormally small, and the cisterna magna is enlarged. Within the posterior vermis only, the declive, folium, and tuber (ie, neocerebellar vermal lobules VI and VII) are particularly maldeveloped and incompletely formed. The remainder of the vermis (ie, anterior vermis, pyramis, nodulus, and uvula—all nonneocerebellar lobules) appears normal in size (midline section; Fig 1, center). The fourth ventricle, folia of the cerebellar hemispheres, and anterior vermal sulci are normal in size. This pattern of abnormal and normal cerebellar features indicates that the abnormalities of the declive, folium, and tuber in the posterior vermis and of the medial neocerebellar hemispheres are attributable to hypoplasia. The dentate nuclei appear to be normal in size.

The right posterior horn of the lateral ventricle is abnormally large, and the right posterior cerebral hemisphere appears to be larger than the left (Figs 2 and 3). Also, in the right posterior cerebral hemisphere (parieto-occipital cortex), there is a slight increase in the sulcal width. Otherwise, cortical structures, including gyral and sulcal landmarks, and cortical thickness appear to be normal (Figs 2 and 3). No abnormalities were found in the anterior or medial temporal lobes, frontal and medial cortical areas, corpus callosum, thalamus, basal ganglia, or brain stem (Fig 2). There are no foci of abnormal signal intensity and no evidence of intracranial lesions (Figs 1 through 3). The lateral (with the exception of the right posterior horn) and third ventricles are normal in size (Figs 2 and 3).

#### COMMENT

With the use of MRI, we have found in vivo evidence of both cerebral and cerebellar abnormalities in a person with a "pure" case of the classic form of infantile autism. This case was uncomplicated by mental retardation, epilepsy, history of drug use, postna-

tal trauma, or disease.

The right posterior cerebral hemisphere appears to be abnormal in this classic case of autism. In particular, the right posterior cerebral hemisphere has an overall size that is larger than its corresponding area on the left hemisphere, which is atypical of normal adult men,<sup>21</sup> and it has an abnormally large ventricle and a slight increase in sulcal width. These findings are not in general agreement with the CT scan data from other nonretarded autistic persons,<sup>10,15</sup> and they raise the question of whether the greater anatomical detail provided by MRI may reveal further evidence of cerebral abnormalities in autism.

The significance of these right posterior cerebral findings is unclear at this time. With anatomical abnormalities of the right posterior cerebral hemisphere, one would predict lower-than-normal nonverbal intellectual ability. Paradoxically, our patient has *higher-than-normal* nonverbal IQ.

The evidence that the right posterior hemisphere is larger than the left in our patient is reminiscent of some CT scan reports, which indicate that some retarded autistic persons have anomalous asymmetries in the parieto-occipital region.<sup>5</sup> Goldman-Rakic and Rakic<sup>22</sup> have shown that removal of one cortical area may result in hypertrophy of the homologous contralateral cortical area, and Geschwind and Galaburda<sup>23</sup> have speculated that poorer development or slowed growth of one cortical area could also result in hypertrophy of the homologous area. One might speculate that the enlarged right posterior hemisphere in our patient is the result of abnormally reduced growth of left hemisphere speech areas associated

with his severe language deficit, particularly during the first six years of his life (the relative contributions to his language deficit of his cerebellar pathologic condition and the functioning in other language areas of his brain cannot be determined). Such a speculation, however, may not be warranted for several reasons; for example, the possibility remains that the right hemisphere enlargement was secondary to right posterior ventricular enlargement, rather than to left hemisphere maldevelopment or underuse. Furthermore, the pathologic data in our patient points to the right cerebral hemisphere, not the left. Our patient's neuropathologic findings remind us that a larger cerebral hemisphere is not necessarily better.

In addition to the cerebral pathologic findings, an unusual cerebellar pathologic condition was found, which appears to be decreased or arrested development of the declive, folium, and tuber in the superior posterior vermis, as well as the medial aspect of the cerebellar hemispheres. The hypoplasia in these three regions of the superior posterior vermis, which constitute neocerebellar vermis, is bracketed on either side by normal-sized anterior vermis and by apparently normal-sized pyramis, nodular, and uvular regions of the inferior posterior vermis.

Very nearly the same structures in the rat have only just recently been shown to be essential for one form of learning and memory—long-term habituation of the acoustic startle response.<sup>24</sup> It is an important experimental question as to whether our patient will show an analogous deficit in long-term habituation.

Such readily noticeable pathologic findings in the cerebellum of our patient do not rule out the possible presence of other pathologic conditions at the microanatomical or physiochemical level that are transparent to the MRI technique. Also, this distinctive single case cannot be used to establish a direct causal link between the cerebellum and autism.

Most importantly, however, this case alerts us to the possibility that the chronology of cerebellar hypoplasias in autism may serve as one signpost pointing to the chronology of the critical neural maldevelopment in autism. For example, the concurrence in our patient of a neuropathologic condition—cerebellar hypoplasia—and a neuropsychopathologic condition—autism—presents the possibility that both pathologic conditions may have resulted from the same

genetically or environmentally mediated disruption to his brain during its development. Because of the nature of our patient's limited gross pathologic findings, we can *hypothesize* critical neurodevelopmental periods during which this pathologic condition could have occurred.

There are several possibilities, three of which will be noted. First, in the rat on developmental day E14, the first Purkinje cells to be generated are destined for the vermal wedge (eventually the posterior vermis) and for portions of the cerebellar hemispheres (the lobus simplex and crura I and II)<sup>25</sup>—regions similar to those that are hypoplastic in our patient. A genetically or environmentally mediated disruption at that time might simultaneously disturb the cytogenesis of these Purkinje cells as well as other neurons whose peak day of neurogenesis is also E14. These latter include neurons of the nucleus reticularis thalami and of the most superficial layer of cortex.<sup>26</sup> Nucleus reticularis thalami gates interactions among cortex, thalamus, and mesencephalic reticular system and is involved in modulating awareness, attention, and sensory transmission.<sup>27-30</sup> Behavioral attention and arousal trigger excitatory input to the most superficial layers of cortex as part of the first stage of cortical activation.<sup>31,32</sup>

As a second example, in the rat, the migrations of Purkinje neurons to posterior and anterior vermis occur in waves, which are separated in time from each other; they migrate first to the posterior vermis (completing their migration from days E17 through E19), and then later to the anterior vermis (completing their migration from days E20 through E22).<sup>25</sup> These migrations occur in a relatively brief time (at the end of the first trimester in the human<sup>33</sup>). A brief disruption at the time of the migration of Purkinje neurons to the posterior vermis could leave it (and the adjacent medial cerebellar hemisphere) hypoplastic, as in our patient; it might also simultaneously affect other neural systems that are undergoing critical development during that time. In the rat, systems undergoing cytogenesis during this period include the subiculum, CA1 and CA3 of the hippocampal formation, portions of the septum, and the amygdalohippocampal area of the corticomедial complex of the amygdala<sup>26</sup>; these neural systems are involved in memory and emotional behavior.

As a third and final example, in humans, granule cell neurogenesis

and migration in the cerebellum occurs throughout the first two years of postnatal life.<sup>34</sup> The declive, folium, and tuber receive their final full complement of granule cells after the anterior vermis and the inferior posterior vermis.<sup>35</sup> If the brain was exposed to teratogenic agents during the final stages of granule cell genesis and migration, depletion of granule cells in the declive, folium, and tuber could occur, but anterior vermis and inferior posterior vermis would be much less affected. Given sufficient granule cell depletion, the macroscopic appearance on MRI scans could be similar to the hypoplasia of the declive, folium, and tuber seen in our patient.

In light of the maternal history, the patient's history, and the appearance of the vermal sulci, a number of potential causes of his cerebellar pathologic condition can be ruled out, including postnatal trauma, epilepsy, nutritional deficiency, maternal use of medications, alcohol or smoking, and maternal endocrine disorders. This patient's abnormal neuroanatomy also differs from known cerebellar developmental anomalies and known degenerative cerebellar diseases.<sup>36-40</sup> For example, his pathologic condition does not present with pontine dysgenesis typical of pontoneocerebellar hypoplasia. Also, in contrast to Down's syndrome, the Dandy-Walker syndrome, the Arnold-Chiari deformity, and the Joubert syndrome, our patient's pathologic condition occurs in the absence of the major malformations of other neuroanatomical and nonneural structures found in these syndromes and in the absence of clinically significant deficits in gross motor functioning. For instance, the Dandy-Walker syndrome includes not only vermal hypoplasia but also enlargement of the fourth ventricle; commonly associated abnormalities include agenesis of the corpus callosum, anomalies of cortical gyri, dolichocephaly, polydactyly, and cleft palate. In congenital cerebellar hypoplasia, the cerebellum is typically uniformly small. This is a rare autosomal recessive disorder in which there is severe reduction in the number of granule cells throughout the cerebellum and neuronal loss in the hippocampus; patients have hypotonia, poor coordination, and delay in motor development—symptoms not seen in our patient.<sup>38-40</sup> At present, we cannot completely rule out some other yet-to-be-described postnatal mechanism that principally affects only portions of the posterior vermis and medial

neocerebellum without concurrently producing overt cerebellar motor dysfunction.

Genetic mutations in mice may provide insights. Postnatal loss of Purkinje cells in mice is caused by two genetic mutations, one called the "nervous" mouse and the other the "PCD" (Purkinje cell degeneration) mouse.<sup>41</sup> Such postnatal Purkinje cell loss might be expected to produce macroscopic cerebellar hypoplasia. Both mouse mutations also cause photoreceptor degeneration. This pattern of pathologic findings—postnatal Purkinje cell loss and photoreceptor degeneration—is distinctive of these genetic mutations. Although our patient exhibits macroscopic hypoplasia, we do not know whether he also has photoreceptor degeneration.

The Purkinje cells of the cerebellar cortex are among the most sensitive in the central nervous system to the effects of anoxia.<sup>42</sup> It is conceivable that anoxia during early development, including postnatal development, could result in an abnormally small cerebellum. However, the medical histories of the mother during pregnancy and of the patient as an infant show no significant event that could cause such a condition. The only wrinkle in the history of the pregnancy was an ordinary cold that the mother had at the end of the first trimester, and the only one in the postnatal period was a three-day cold with a temperature of 39.4°C that the patient had at 22 months of age.

Dysprosody may result from cerebellar damage in adulthood, particularly to the left superior paravermal cerebellum<sup>43</sup> (for a review, see reference 37). In global cerebellar hypoplasia, speech typically fails to develop,<sup>39,40</sup> and, when it does, it has been described as hesitant, stammering, and explosive in character.<sup>39</sup> It seems likely that our patient's dysprosody is a consequence of his regional cerebellar hypoplasia. If that were so, one may speculate that cerebellar mechanisms are crucial to the development of speech and that neural plasticity is insufficient to fully compensate for some speech deficits resulting from a cerebellar pathologic condition incurred early in development—in contradistinction to the Kennard principle, which states that there is greater recovery or sparing of function following lesions incurred early in development compared with those incurred later.<sup>44,45</sup> In contrast to speech, it is curious and noteworthy that the cerebellar pathologic features in our patient were not associated with

impairment of other aspects of motor development.

Thus, our patient represents an unusual case of regional cerebellar hypoplasia. Patients with global cerebellar hypoplasia usually exhibit global cognitive impairment, delays or failure to develop speech, hesitant and explosive speech, and the following major motor abnormalities: substantial delays in or failure to sit, stand, or walk; hypotonia; incoordination (eg, ataxia, dyssynergia, and titubation); and abnormal ocular movements (eg, fixation nystagmus).<sup>39,40</sup> In comparison, our patient has partial cognitive impairment, was delayed in speech development, has hesitant and explosive speech, did not have major motor abnormalities beyond dysprosody and poor balance with eyes closed, and has autism.

The cerebellar pathologic findings in our nonretarded patient are consistent with previous CT as well as post-mortem neuropathologic data from several severely retarded autistic persons.<sup>17,18</sup> A question raised by these findings is whether cerebellar anatomical abnormalities, having now been found in retarded and nonretarded autistic individuals alike, may be found in a significant subpopulation of autistic persons in general. Another question is the part played by anatomical abnormalities of the cerebellum when it does occur in persons with autism. It has been suggested that these abnormal cerebellar anatomical and physiologic conditions might significantly disrupt the functioning of attentional mechanisms,<sup>46</sup> the limbic system,<sup>47</sup> and the acquisition and execution of skilled mental as well as motor operations.<sup>48</sup> Recently, the cerebellum has been shown to be an essential location for certain forms of learning and memory.<sup>24,49</sup> For instance, might anatomical abnormalities in the vermis in autism affect long-term habituation of the acoustic startle response as it does in rats,<sup>24</sup> or might anatomical abnormalities of the cerebellar hemispheres in autism affect associative learning as it does in rats?<sup>49</sup>

The answer to these questions will require MRI studies of larger samples of retarded and nonretarded autistic persons, and comparing subjects with major cerebellar pathologic findings, as seen in MRI data, with those without discernible pathologic findings in detailed neurophysiologic, neurochemical, and behavioral studies.

This research was supported by Children's Hospital Research Center, San Diego, and by

grant 5-R01-NS19855 from the National Institute of Neurological and Communicative Disorders and Stroke and grant 1-R01-MH36840 from the National Institute of Mental Health, National Institutes of Health, Bethesda, Md (Dr Courchesne).

Valuable assistance has also been provided by the Magnetic Resonance Institute of the Medical Center of the University of California at San Diego and by the San Diego Regional Center for the Developmentally Disabled. We extend special thanks to Sara Wells, Alan J. Lincoln, PhD, and Beverly A. Kilman, PhD.

## References

1. Kanner L: Autistic disturbances of affective contact. *Nerv Child* 1943;2:217-250.
2. Cohen DJ, Caparulo B, Shaywitz B: Primary childhood aphasia and childhood autism: Clinical, biological and conceptual observations. *J Am Acad Child Psychiatry* 1976;15:604-645.
3. Rutter M: Language, cognition, and autism, in Katzman R (ed): *Congenital and Acquired Cognitive Disorders*. New York, Raven Press, 1979, pp 247-264.
4. DeMyer MK, Hingtgen JN, Jackson RK: Infantile autism reviewed: A decade of research. *Schizophr Bull* 1981;7:388-451.
5. Hier DB, LeMay M, Rosenberger PB: Autism and unfavorable left-right asymmetries of the brain. *J Autism Dev Disord* 1979;9:153-159.
6. Campbell M, Rosenbloom S, Perry R, et al: Computerized axial tomographic scans in young autistic children. *Am J Psychiatry* 1982;139:510-512.
7. Damasio H, Maurer RG, Damasio AR, et al: Computerized tomographic scan findings in patients with autistic behavior. *Arch Neurol* 1980;37:504-510.
8. Caparulo BK, Cohen DJ, Rothman SL, et al: Computed tomographic brain scanning in children with developmental neuropsychiatric disorders. *J Am Acad Child Psychiatry* 1981;20:338-357.
9. Tsai L, Jacoby C, Stewart M, et al: Unfavorable left-right asymmetries of the brain and autism: A question of methodology. *Biol Psychiatry* 1983;18:317-327.
10. Prior MR, Tress B, Hoffman WL, et al: Computed tomographic study of children with classic autism. *Arch Neurol* 1984;41:482-484.
11. Prior M: Learning abilities and disabilities in childhood autism: A review. *J Abnorm Child Psychol* 1979;7:357-380.
12. Hoffman W, Prior M: Neuropsychological dimensions of autism in children: A test of the hemispheric dysfunction hypothesis. *J Clin Neuropsychol* 1982;4:27-42.
13. Rumsey JM, Grimes AM, Pikus AM, et al: Auditory brainstem responses in pervasive developmental disorders. *Biol Psychiatry* 1984;19:1403-1418.
14. Courchesne E, Yeung-Courchesne R, Hicks G, et al: Functioning of the brainstem auditory pathway in non-retarded autistic individuals. *Electroencephalogr Clin Neurophysiol* 1985;61:491-501.
15. Creasey H, Rumsey JM, Schwartz M, et al: Brain morphology, as measured by quantitative CT scanning, in autistic men. *Arch Neurol* 1986;43:669-672.
16. Williams RS, Hauser SL, Purpura DP, et al: Autism and mental retardation: Neuropathologic studies performed in four retarded persons with autistic behavior. *Arch Neurol* 1980;37:749-753.
17. Jaeken J, van den Berghe G: An infantile autistic syndrome characterized by the presence of succinylpurines in body fluids. *Lancet* 1984;1:1058-1059.
18. Bauman M, Kemper TL: Histoanatomic observations of the brain in early infantile autism. *Neurology* 1985;35:866-874.

19. Hagberg B, Aicardi J, Dias K, et al: A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: Report of 35 cases. *Ann Neurol* 1983;14:471-479.

20. Rutter M: Language disorder and infantile autism, in Rutter M, Schopler E (eds): *Autism: A Reappraisal of Concepts and Treatment*. New York, Plenum Publishing Corp, 1978.

21. Zatz LM, Jernigan TL, Ahumada AJ: Changes on computed cranial tomography with aging: Intracranial fluid volume. *Am J Neuroradiol* 1982;3:1-11.

22. Goldman-Rakic P, Rakic P: Experimental modification of gyral patterns, in Geschwind N, Galaburda AM (eds): *Cerebral Dominance: The Biological Foundations*. Cambridge, Mass, Harvard University Press, 1984, pp 179-192.

23. Geschwind N, Galaburda AM: Cerebral lateralization: Biological mechanisms, associations, and pathology: II. A hypothesis and a program for research. *Arch Neurol* 1985;42:521-552.

24. Leaton RN, Supple WF: Cerebellar vermis: Essential for long-term habituation of the acoustic startle response. *Science* 1986;232:513-515.

25. Altman J, Bayer SA: Embryonic development of the rat cerebellum: III. Regional differences in the time of origin, migration, and settling of Purkinje cells. *J Comp Neurol* 1985;231:42-65.

26. Bayer SA, Altman J: Directions in neuro-genetic gradients and patterns of anatomical connections in the telencephalon. *Prog Neurobiol*, in press.

27. Scheibel AB: Anatomical and physiological substrates of arousal: A view from the bridge, in Hobson JA, Brazier MAB (eds): *The Reticular Formation Revisited*. New York, Plenum Publishing Corp, 1980, pp 55-66.

28. Watson RT, Valenstein E, Heilman KM: Thalamic neglect: Possible role of the medial thalamus and nucleus reticularis in behavior. *Arch Neurol* 1981;38:501-506.

29. Skinner JE, Yingling CD: Regulation of slow potential shifts in nucleus reticularis thalami by the mesencephalic reticular formation and the frontal granular cortex. *Electroencephalogr Clin Neurophysiol* 1976;40:288-296.

30. Singer W: Control of thalamic transmission by corticofugal and ascending reticular pathways in the visual system. *Physiol Rev* 1977;57:386-420.

31. Inubushi S, Kobayashi T, Oshima T, et al: Intracellular recordings from the motor cortex during EEG arousal in unanesthetized brain preparations of the cat. *Jpn J Neurophysiol* 1978;28:669-688.

32. Inubushi S, Kobayashi T, Oshima T, et al: An intracellular analysis of EEG arousal in cat motor cortex. *Jpn J Neurophysiol* 1978;28:689-708.

33. Rakic P, Sidman RL: Histogenesis of cortical layers in human cerebellum, particularly the lamina dissecans. *J Comp Neurol* 1970;139:473-500.

34. Raaf J, Kernohan JW: A study of the external granular layer in the cerebellum. *Am J Anat* 1944;75:151-172.

35. Altman J: Autoradiographic and histological studies of postnatal neurogenesis: III. Dating the time of production and onset of differentiation of cerebellar microneurons in rats. *J Comp Neurol* 1969;136:269-294.

36. Malamud N, Hirano A: *Atlas of Neuropathology*. Berkeley, University of California Press, 1974.

37. Gilman S, Bloedel J, Lechtenberg R: *Disorders of the Cerebellum*. Philadelphia, FA Davis Co Publishers, 1981.

38. Chaves E, Frank LM: Disorders of basal ganglia, cerebellum, brain stem, and cranial nerves, in Farmer TW (ed): *Pediatric Neurology*. New York, Harper & Row Publishers Inc, 1983, pp 605-648.

39. Jervis GA: Early familiar cerebellar degeneration. *J Nerv Ment Dis* 1950;111:398-407.
40. Sarnat HB, Alcalá H: Human cerebellar hypoplasia: A syndrome of diverse causes. *Arch Neurol* 1980;37:300-305.
41. Caviness VS Jr, Rakic P: Mechanisms of cortical development: A view from mutations in mice. *Ann Rev Neurosci* 1978;1:297-326.
42. Margerison JH, Corsellis JAN: Epilepsy and the temporal lobes. *Brain* 1966;89:499-530.
43. Lechtenberg R, Gilman S: Speech disorders in cerebellar disease. *Ann Neurol* 1978;3:285-

290.

44. Simons D, Finger S: Some factors affecting behavior after brain damage early in life, in Finger S, Almlí CR (eds): *Early Brain Damage*. Orlando, Fla, Academic Press Inc, 1984, vol 2: *Neurobiology and Behavior*, pp 327-347.
45. Will B, Eclander F: Early brain damage and early environment, in Finger S, Almlí CR (eds): *Early Brain Damage*. Orlando, Fla, Academic Press Inc, 1984, vol 2: *Neurobiology and Behavior*, pp 349-367.
46. Courchesne E: A neurophysiological view of autism, in Schopler E, Mesibov GB (eds):

*Neurobiological Issues in Autism*. New York, Plenum Publishing Corp, 1986.

47. Heath R, Dempsey CW, Fontana CJ, et al: Feedback loop between cerebellum and septal-hippocampal sites: Its role in emotion and epilepsy. *Biol Psychiatry* 1980;15:541-556.
48. Leiner HC, Leiner AL, Dow RS: Does the cerebellum contribute to mental skills? *Behav Neurosci* 1986;100:443-454.
49. McCormick DA, Thompson RF: Cerebellum; Essential involvement in the classically conditioned eyelid response. *Science* 1984; 223:296-299.

## Sporadic Case Resembling Autosomal-Dominant Motor System Degeneration (Azorean Disease Complex)

Barbara A. McQuinn, MD, Thomas L. Kemper, MD

● We describe a case of an adult-onset progressive dystonia with external ophthalmoplegia, occurring in a black man without a family history of neurologic disorders. Neuropathologic examination demonstrated neuronal loss and gliosis in the anterior horn and Clarke's column in the spinal cord, nuclei of cranial nerves III, VI, X, and XII, vestibular complex, lateral cuneate nucleus, lower pontine tegmentum, red nucleus, substantia nigra, and dentate nucleus. The cerebral cortex, corpus striatum, basis pontis, inferior olives, and cerebellum were spared. The clinical and pathologic findings closely resemble autosomal-dominant motor system degeneration or "Azorean disease," without, however, demonstrable familial transmission. In addition to the absence of a family history, unique features of the case include the presence of Alzheimer type II glial cells in the red nucleus and an unexplained persistent elevated concentration of serum amylase.

(*Arch Neurol* 1987;44:341-344)

Autosomal-dominant motor system disease (ADMSD) is a dominantly inherited, progressive, and unremitting disorder, originally described in patients of Portuguese Azorean descent<sup>1-5</sup>; hence, the term *Azorean disease of the nervous system*. It has been described in at least four Portuguese families, two black families, and one Japanese family.<sup>6,9</sup> The clinical manifestations include dystonia and/or rigidity, ataxia, progressive external ophthalmoplegia, dysarthria, amyotrophy, extensor plantar re-

sponses, and variable cranial nerve abnormalities. At autopsy, affected family members exhibited consistent neuronal loss in the anterior horns and Clarke's column in the spinal cord, the cranial nerve motor nuclei concerned with extraocular motility, hypoglossal nucleus, vestibular complex, and substantia nigra in the brain stem, and in the dentate nucleus of the cerebellum (Table). We describe herein the clinical features and neuropathology of what is the first, to our knowledge, sporadic case of the disease.

### REPORT OF A CASE

A 38-year-old black man, born and raised in Barbados, died of aspiration pneumonia following a protracted and progressive neurologic illness. His difficulties began at age 21 years, when his sister first noted an unsteady gait and buckling of his left knee. At age 23 years, he began to experience involuntary writhing movements of the limbs and trunk, necessitating his confinement to a wheelchair by age 25 years. At age 30 years, a neurologic examination demonstrated slurred speech, truncal ataxia, mild dysmetria in the left arm on finger-to-nose testing, and left hemiparesis. He was admitted later that year to another hospital for evaluation of abdominal pain. Neurologic evaluation disclosed further progression of his disease, with limitation of upgaze, nystagmus on lateral gaze in either direction, mild ptosis, saccadic pursuit of visual stimuli, generalized choreoathetosis, vermiform movements of the tongue, and increased tone with bilateral extensor plantar responses. His abdominal pain resolved spontaneously. A thorough gastrointestinal work-up was unremarkable except for an elevated serum amylase concentration (234 Somoogy U/dL [433 U/L]), which persisted in this range throughout the rest of his life. Three years later, the patient was admitted for spontaneous left arm and hand

dysesthesias due to a left C6-C7 cervical radiculopathy, and the recent onset of a leftward torticollis. Severe athetosis of the limbs that could be provoked by either voluntary movements or by strong emotion was noted. The extraocular movement findings were unchanged. A mild left facial paresis and myokymia over the left eyelid and corner of the mouth was apparent. Strength, cognitive function, perception of pinprick, light touch, and vibration were normal. Muscle tone was now decreased, and his speech had become hypophonic. Plantar responses were recorded as flexor. An electrodiagnostic evaluation demonstrated a mild, diffuse peripheral neuropathy.

In the next five years, the patient's external ophthalmoplegia had progressed to such a degree that no eye movements in any direction could be elicited either voluntarily or by oculovestibular testing maneuvers. Bilateral ptosis was present and the pupils reacted sluggishly to light. The gag reflex was absent. The patient's speech was unintelligible although he was able to follow complex commands. Reflexes were brisk bilaterally and his plantar reflexes were again extensor. The patient suffered a respiratory arrest and died 17 years after the onset of symptoms.

Pharmacologic therapy was attempted repeatedly during the course of his illness. Levodopa/carbidopa, baclofen, amantidine hydrochloride, and several anticholinergic agents were ineffective in alleviating his dystonia.

The family history, obtained from old hospital records and available family members, was negative for neurologic or psychiatric illness. The patient's relatives denied a history of either known consanguinity or Azorean ancestry. His mother died at age 53 years while still in Barbados, reportedly from complications of diabetes mellitus. His father is alive and well at age 70 years. None of the patient's family reported any history of neurologic problems, gait trouble, tremors, or early death in themselves or other relatives, although diabetes mellitus was common on the

Accepted for publication Oct 20, 1986.

From the Neurological Unit, Boston City Hospital, Boston.

Reprint requests to 2832 Summit St, Oakland, CA 94609 (Dr McQuinn).