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Brain Atrophy in 18 Patients with Down Syndrome: A CT Study

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Individuals with Down syndrome develop neuropathologic and in some cases clinical evidence of Alzheimer disease after age 40. We compared CT scans of 18 Down syndrome subjects, 26–70 years old (seven of whom satisfied criteria for dementia), with 175 screened normal volunteer control subjects for evidence of cortical and subcortical atrophy. CT scans were analyzed as a function of age and cognitive status. The suprasellar cistern ratio, presumed to measure mesial temporal-lobe atrophy (or hypoplasia), was correlated with severity of cognitive impairment, even when age effects were removed. The suprasellar cistern ratio predicted dementia status with an accuracy of greater than 75%.

Brain measurements on CT scans showed a distinct pattern of increased abnormality with age in patients with Down syndrome; this differed clearly from that seen in controls.

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Individuals with Down syndrome (DS) are at high risk for the early onset of Alzheimer disease (AD) [1–8]. One major survey [9, 10] found the neuropathology of AD in 50% of DS subjects over 35 years of age and in 100% of subjects over 40 years of age. This neuropathology has been described as quantitatively and qualitatively similar to that of AD in individuals without mental retardation [8, 11–14]. Clinical deterioration with memory loss, apraxia, and anomia has been reported in some individuals with DS [15–18], most obviously in older DS subjects [16, 19–26]. These changes have been attributed to the development of AD. In vivo studies using positron emission transverse tomography also suggest that changes similar to those of AD occur in DS individuals [26].

Not all individuals with DS develop dementia at ages when they reportedly develop the neuropathology; approximately 30% do so by age 40 [2, 5, 7, 18, 19, 21, 27–35]. Individuals with DS therefore provide an unusual opportunity to study the evolution of this neuropathology and its relationship to clinical dementia, if accurate in vivo measures of neuropathology can be determined. In individuals who are not mentally retarded, attempts have been made to use brain CT measures in this manner [36–52]. LeMay et al. [52] showed that mesial temporal CT measures (especially of the suprasellar cistern) best distinguished AD subjects from controls. Even early in the disease, mesial temporal structures, such as hippocampus and amygdala, are universally and severely affected by the neuropathology of AD [38]. We hypothesized that mesial temporal CT measures would provide a sensitive measure of AD neuropathology in DS during life. Several previous CT studies examined DS subjects [53–55]; some aspects of the relationship of brain atrophy to aging and dementia in DS still need clarification (for example, the importance of preexisting cerebral hypoplasia [56]).

No study has examined the suprasellar cistern in DS. Because at least one previous study [55] reported cerebral atrophy in institutionalized DS patients, we were interested in seeing if similar changes occurred in a population of community-

dwelling subjects. Therefore, we examined a series of regional brain CT measures in demented and nondemented DS subjects of various ages, as a function of patient age and cognitive status.

Subjects and Methods

DS Subjects

We examined 18 community-dwelling subjects with DS whose diagnosis was confirmed by karyotype. All had been followed longitudinally in a DS clinic. These patients were representative of the DS clinic population: 68 individuals 36 ± 10 years old (mean \pm SD); Mini Mental State Examination (MMSE) [57] score, 13.2 ± 9.9 . The DS subjects in our study were 26–70 years old (mean, 42 ± 12 years); eight were less than 40 years old. MMSE scores ranged from 0 to 26 (mean, 11.2 ± 10.2). Seven subjects had clinical dementia, demonstrated by a history of behavioral deterioration, plus significant decrements on the Adaptive Behavior Scale of the American Association of Mental Deficiency [58] and the Disability Assessment Schedule of Holmes et al. [59]. All seven were initially well enough to have been community dwelling and independent in activities of daily living. Following the onset of dementia, all became progressively disabled, eventually requiring total care. In addition, all demented individuals showed continuing longitudinal declines in MMSE scores (although predementia baseline MMSE scores were not available in every case). The mean MMSE score in the demented DS subjects ($n = 7$) was 2.3 ± 5.6 ; in the nondemented ($n = 11$), 16.8 ± 8.7 . Corresponding ages were 48 ± 13 and 38 ± 10 years; six demented and four nondemented individuals were more than 40 years old.

Normal Control Subjects

Normal control subjects consisted of 175 individuals 19–87 years old who were employees of the Johns Hopkins Hospital or their relatives, or persons who responded to a series of advertisements in hospital and local newspapers. None had a personal history of

psychiatric illness or psychiatric hospitalization. Exclusion criteria for controls included any history of CNS illness, head injury causing loss of consciousness for longer than 1 hr, headaches of sufficient severity to have led to medical consultation, heavy alcohol or street drug use in the last 12 months, oral steroid use in the preceding 3 months, loss of 25% or more of original body weight in the last 12 months, or current pregnancy. All scored 27 or above on the MMSE.

CT Study

Unenhanced axial CT scans were obtained in all subjects. A single Siemens Somatom DR-3 CT scanner (Siemens Medical Systems, Iselin, NJ) and 512×512 matrix were used, as previously described by our group [41]. Scanning parameters were kept constant, and a specially designed head holder was used to ensure a fixed scanning angle. Standard 8-mm cuts, at 0° to the supraorbital-meatal line, were taken through the entire brain. Informed consent was obtained from all subjects (in the case of DS patients, from parents or guardians) after the nature of the procedure was fully explained. Both patients and control subjects were scanned at each imaging session to eliminate possible systematic bias; a single CT technologist performed all scanning. Scans assessed by a neuroradiologist as showing artifact were rejected. Scans were then measured blindly with respect to diagnosis, after enlargement by the reciprocal of the scan minification factor, using an overhead radiographic projector. To maintain blindness to diagnosis, patient and control scans were assessed randomly, mixed with those of subjects from several other CT studies.

Five measures of cerebral atrophy (or hypoplasia) were used (one cortical and four subcortical); these were derived from previous studies of neuropsychiatric disorders [52, 60–63]:

1. *Lateral ventricle-to-brain ratio (VBR)* [60]. This measure of subcortical atrophy was blindly measured planimetrically at the widest point of the bodies of the lateral ventricles, as previously described by our group [41]. Retracings of lateral VBRs by the same or different raters were reliable ($r = .94$). Remeasurement of the tracings by planimeter was also replicable ($r = .99$).

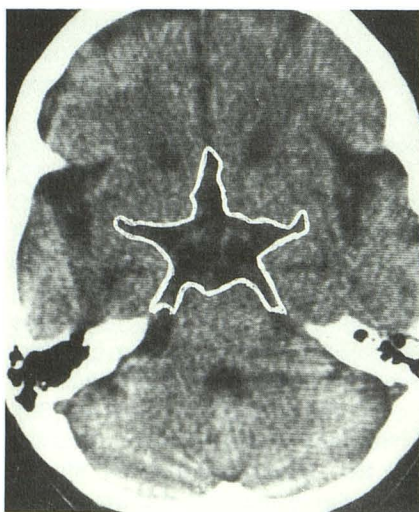


Fig. 1.—Representative cranial CT cut shows suprasellar cistern (outlined to show borders). This area was used as the numerator in determining the suprasellar cistern ratio.

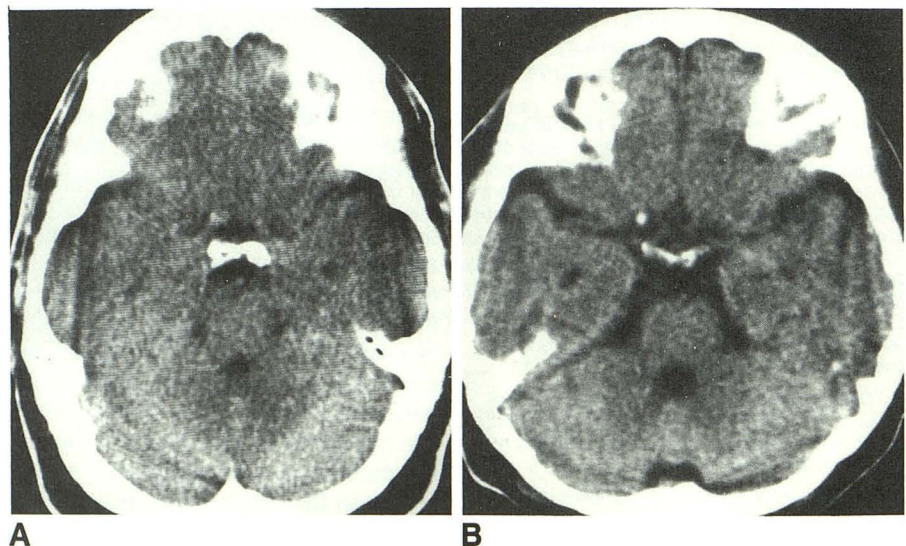


Fig. 2.—A, Down syndrome subject without dementia. Suprasellar cistern ratio (SSCR) fell within control range.
B, Down syndrome subject with dementia. SSCR was >2 SD outside age-appropriate control range.

2. *Cortical sulcal atrophy (CSA)* [61]. This analog measure of cortical atrophy was assessed from the CT cut two slices above the lateral ventricles at their widest. Four ratings were assigned: 1 = no atrophy; 2 = mild atrophy; 3 = moderate atrophy; 4 = severe atrophy. Fifteen scans were rated independently by one rater on two separate occasions; intrarater reliability (Spearman [64]) was $r = .89$.

3. *Bifrontal ratio (BFR)* [62, 63]. This measure of anterior subcortical atrophy was defined as the distance between the tips of the frontal horns divided by the distance between the inner tables of the skull along the same line. Reliability (interrater) for 15 scans was $r = .93$.

4. *Bicaudate ratio (BCR)* [62, 63]. This measure of caudate atrophy was defined as the minimal distance between the caudate indentations of the frontal horns divided by the distance between the inner tables of the skull along the same line. Reliability (interrater) for 15 scans was $r = .91$.

5. *Suprasellar cistern ratio (SSCR)* (modified from LeMay et al. [52] by conversion to a ratio measurement). This measure of mesial temporal-lobe atrophy was defined as the planimetric area of the suprasellar cistern, divided by planimetric brain area at the level of the foramen of Monro. The latter area was used because brain area at the level of the suprasellar cistern often was marred by bony artifact. Reliability (interrater) for 15 scans was $r = .94$.

Figure 1 illustrates the level chosen for rating and an outline of the portion of the suprasellar cistern used for the SSCR measure. Figure 2 compares representative suprasellar cisterns of demented and cognitively normal DS patients.

Neurocognitive measurements.—The MMSE [57] was chosen because of its simplicity and suitability for DS patients.

Results

The control subjects were divided into groups by age (in decades). Means (\pm SD) were calculated for each of the four nonanalog CT atrophy measures for each group (Figs. 3–6). Individual DS values are displayed relative to these.

Figure 3 shows reference values of SSCR vs age (in decades) derived from normal controls. Similar plots are shown for VBR (Fig. 4), BCR (Fig. 5), and BFR (Fig. 6).

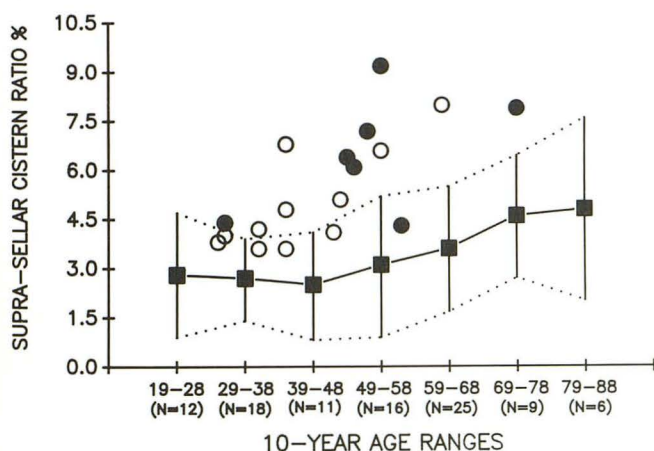


Fig. 3.—Plot of suprasellar cistern ratio vs age. In normal control subjects (squares), values 2 SD above and below each mean are indicated by bars and joined by dotted lines. Values are given for individual Down syndrome subjects with (solid circles) and without (open circles) dementia.

Mesial temporal size in DS subjects, as judged by the SSCR, was clearly reduced from that in control subjects beginning around age 30. Other atrophy measures showed a similar tendency to be increased relative to normals, but occurring at a later age than for SSCR.

In DS, the SSCR was the CT measure most frequently abnormal; that is, >2 SD outside the age-appropriate mean. This was so for DS subjects less than 40 years old (50% abnormal as defined above), more than 40 years old (80% abnormal), or with dementia (86% abnormal). VBR, BCR, and BFR identified correspondingly lower percentages of DS as abnormal in each of the above diagnostic categories; for DS with dementia, the percentages so classified were 71%, 71%, and 43%, respectively.

For the analog measure of CSA, the two least and two most severe ratings were collapsed to yield dichotomous,

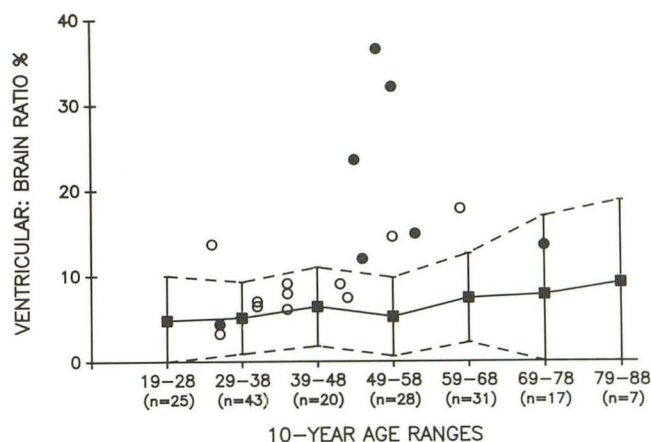


Fig. 4.—Plot of ventricle-to-brain ratio vs age. In normal control subjects (squares), values 2 SD above and below each mean are indicated by bars and joined by dotted lines. Values are given for individual Down syndrome subjects with (solid circles) and without (open circles) dementia.

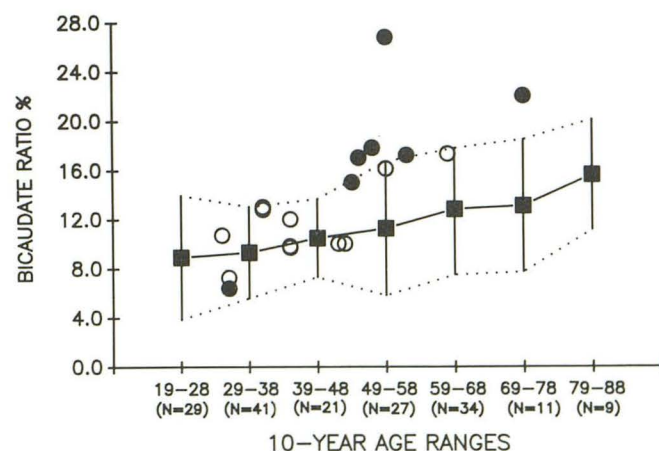


Fig. 5.—Plot of bicaudate ratio vs age. In normal control subjects (squares), values 2 SD above and below each mean are indicated by bars and joined by dotted lines. Values are given for individual Down syndrome subjects with (solid circles) and without (open circles) dementia.

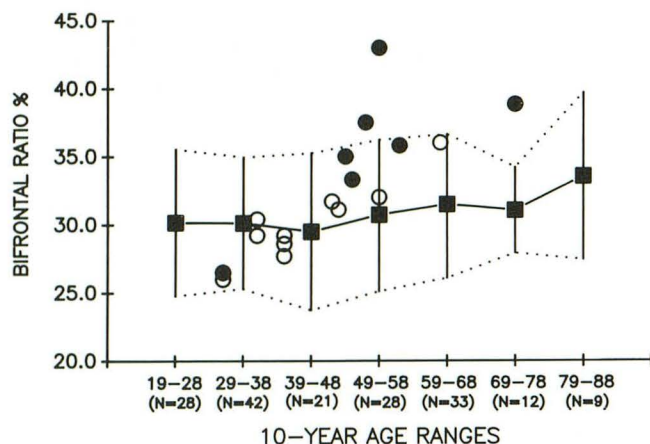


Fig. 6.—Plot of bifrontal ratio vs age. In normal control subjects (squares), values 2 SD above and below each mean are indicated by bars and joined by dotted lines. Values are given for individual Down syndrome subjects with (solid circles) and without (open circles) dementia.

easily tabulated values. Below age 39, no control ($n = 42$) or DS ($n = 8$) subjects had values of 3 or 4 (corresponding to moderate or severe atrophy). Between ages 39 and 78, 16 of 58 control and seven of 10 DS subjects had ratings of 3 or 4 (Yates corrected chi-square = 5.1 [1 df]; $p < .05$). Six of the seven demented DS patients had CSA ratings of 3 or 4.

Relationships between CT measures and cognition and age were examined. Of all CT ratings in DS ($n = 18$), the SSCR correlated most highly with cognitive status (judged by MMSE scores), at $r = -.91$ ($p < .01$). VBR correlated with MMSE scores at $r = -.57$ ($p < .05$), BCR at $r = -.67$ ($p < .01$), and BFR at $r = -.66$ ($p < .01$). SSCR was also most highly correlated with patient age ($r = .78$, $p < .01$), followed by BFR, BCR, and VBR, with values of $.70$ ($p < .01$), $.59$ ($p < .05$), and $.24$ (NS), respectively.

A discriminant function analysis was carried out using SSCR to predict the presence or absence of dementia. Fourteen of 18 DS subjects were correctly classified (six of seven demented, eight of 11 nondemented).

Because demented DS patients tended to be older, we carried out a statistical analysis to separate out effects of aging from those of dementia. A multiple regression analysis was carried out for DS subjects, with age, SSCR, BFR, BCR, and VBR as independent variables and MMSE as the outcome. The best predictor of MMSE when a forced-entry model was used was SSCR (F to remove = 2.44). Age was the best predictor of MMSE only when SSCR was absent from the model. In a univariate analysis with MMSE, SSCR alone had an r^2 of .69. When a regression was carried out on age, the r^2 was .44, with the partial correlation of SSCR being $-.67$. For the reverse situation, the r^2 for SSCR was .73, with the partial correlation of age being $-.12$; that is, age influences MMSE through its effect on SSCR. SSCR retained its predictive power for MMSE when adjusted for age, but the converse was not true.

Discussion

Our results indicate that several CT alterations are observed more frequently in community-dwelling individuals with DS than in non-mentally retarded normal individuals of similar age. These various changes are consistent with brain atrophy or hypoplasia of mesial temporal, caudate, anterior subcortical, and generalized cortical and subcortical regions. We found such changes to become particularly prominent after age 40, and with the development of dementia. These CT measures have consequences in behavior in that they correlate with a summary measure of cognitive status in both demented and nondemented DS individuals.

The SSCR, a measure of mesial temporal size, has previously been demonstrated to discriminate well between normal age-matched controls and patients with AD [52]. In our study of DS, it was the earliest measure to vary from control values, suggesting that structures in this region are involved at an early stage. It does not address the question of exactly when in DS the neuropathologic changes of AD begin. It is consistent with the Pearson-Powell hypothesis [65]. The SSCR correlated most highly with cognitive function in DS individuals as measured by MMSE scores. The SSCR discriminated demented from nondemented DS individuals with fair accuracy (78% correctly classified). The SSCR correlated highly with severity of cognitive impairment in DS, even when effects of age were removed. Our sample sizes were not sufficient to establish fully whether CT measurements could validly identify dementia in DS patients.

There have been several previous CT studies of DS patients [53–55]. Two studies did not find disproportionate changes in DS compared with controls in ventricular volume [53] or BCR [54]. However, these studies, especially one of them [54], used predominantly young subjects; others used group comparisons or did not employ ratio measures to correct for smaller brain size in DS. The latter factor is important, as even young DS subjects show small brains, most likely owing to both reduced head size related to height [53] and abnormal brain development (as summarized by Zellweger [56]). Other studies have demonstrated generalized cortical atrophy in younger DS subjects [55], which was severe and progressive in a small number of subjects with dementia [15].

Our results differ from those of Schapiro et al. [53] in demonstrating the presence of disproportionate atrophy in DS subjects. However, only seven DS patients in that report were older than 35, and of these only one was demented. Their methods also differed from those of our study, in using absolute measures for intracranial assessment rather than ratios correcting for smaller brain size. Comparisons in their study were by group; in ours, by decade. They assessed CSF volume as a whole; we used separate cortical and subcortical measures.

By contrast, the prevalence of atrophy we found on CT is less than that reported by Wisniewski et al. [55], most likely because we did not use an institutionalized population. Our results are more consistent with those of the group [7, 8] that assessed postmortem brain weight in DS compared with controls. In that study, 47% of DS patients younger than 40

had values ≥ 2 SD lower than controls, compared with 90% of DS patients older than 40.

In this cross-sectional study, despite a small sample size, we are confident that we demonstrated significant anatomic brain changes in DS subjects during life (as opposed to postmortem studies); these were present in most subjects by age 30. Future studies should attempt to address the specificity of various linear and area measures in distinguishing between larger series of demented and nondemented DS patients. Ideally, they should be longitudinal and prospective in nature, with ultimate neuropathologic confirmation, in order to clarify the order of emergence of brain changes relative to onset of dementia. It remains to be seen whether atrophic changes similar to the ones described here eventually emerge in all cases of DS. MR (particularly with thin coronal cuts through temporolimbic structures) may also be helpful in delineating the specificity of regional anatomic changes compared with those of AD.

An interesting finding was that even the younger DS individuals had some mesial temporal atrophy on CT, although most were still within normal limits. CT or MR scans in a larger and even younger sample than ours would address the question of whether such changes are congenital or degenerative in nature.

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