Measuring atrophy in Alzheimer disease

A serial MRI study over 6 and 12 months

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Abstract—*Background:* Global brain atrophy rate calculated from serial MRI scans may be a surrogate marker of Alzheimer disease (AD) progression. Few studies have assessed atrophy in AD over short intervals. *Methods:* Thirty-eight patients with AD and 19 control subjects had MRI scans at baseline, 6 months, and 1 year. Ventricular change and whole-brain volume loss were calculated directly from the regions manually outlined on registered scans and using the automated (boundary shift integral [BSI]) technique. Sample sizes required to power placebo-controlled treatment trials over 6 months and 1 year were calculated using these techniques. *Results:* Increased rates of ventricular expansion and whole-brain atrophy were seen in AD compared with control subjects at both 6 and 12 months using manual and automated techniques ($p < 0.001$). Using the BSI consistently reduced measurement variability especially for whole-brain change. In clinical trials, at 6 months, significantly fewer patients would be required using the ventricular BSI (VBSI) compared with the brain BSI (BBSI) (e.g., 165 vs 410 per arm to provide 90% power to detect a 20% reduction in rate of change). At 1 year, sample size estimates were smaller than at 6 months, and the advantage of using VBSI instead of BBSI was less marked. *Conclusions:* In short-interval studies, using the ventricular boundary shift integral instead of the brain boundary shift integral may allow for disease-modifying effects to be demonstrated using significantly smaller sample sizes. This potential benefit must be balanced against the possibility that ventricular volumes may be more likely to be affected by factors other than neurodegeneration.

NEUROLOGY 2005;65:119–124

Major efforts are under way to develop disease-modifying agents for Alzheimer disease (AD); outcome measures that can distinguish disease-modifying from symptomatic effects are therefore urgently required. Cerebral atrophy may be one such measure: a truly disease-modifying drug would be expected to slow excess atrophy in AD compared with placebo. Rates of global brain atrophy may be calculated in vivo from registered serially acquired MRI scans using either brain volume loss[1-5] or ventricular expansion[4-7] (table 1). To date, all but one[4] of these studies assessing atrophy rates in AD have done so over periods of ≥1 year. In this study, we assessed direct (boundary shift integral [BSI])[1,8,9] and indirect (outlining) measures of brain volume and ventricular change in cohorts of patients with AD and normal control subjects studied prospectively over periods of 6 months and 1 year and estimated the effect of using ventricular and brain-based measures of atrophy on sample sizes that would be required in clinical trials over 6 months and 1 year.[2] By comparing relative rates of brain and ventricular change in patients and control subjects, we also aimed to evaluate factors influencing the dynamics of whole-brain atrophy.

Methods. Ethical approval for the study was received from the local research ethics committee. Subjects gave written informed consent and underwent a comprehensive clinical assessment including the Mini-Mental State Examination (MMSE).[10] Thirty-eight patients with probable AD were recruited from the Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery, where they had all been fully investigated; 19 control subjects were also recruited.

Entry criteria for all subjects were age >55, no contraindications to MR scanning, and tolerability of the first scan. AD patients fulfilled National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria[11] for the diagnosis of probable AD and had an MR scan compatible with this clinical diagnosis and a MMSE score of >12 and <27. Treatment with an acetylcholinesterase inhibitor was not an exclusion criterion. Control subjects all had an MMSE score of ≥27 and no subjective complaints or objective evidence of cognitive impairment.

MRI scanning was performed on a 1.5 T Signa unit (GE Medical Systems, Milwaukee, WI). T1-weighted volumetric images were obtained using a spoiled fast GRASS sequence technique with a 24-cm field of view and 256 × 256 matrix to provide 124 contiguous 1.5-mm-thick slices in the coronal plane. The scan acquisition parameters were as follows: repetition time = 15 milliseconds; echo time = 5.4 milliseconds; flip angle = 15°; inversion time = 650 milliseconds. Each patient was scanned at baseline, at 6 months, and at 1 year. Scans were performed on the same scanner, using the same acquisition parameters, and each subject was scanned at a consistent time of day. No subject was taking diuretic therapy during the study, and no subject drank alcohol to excess.

Image data were transferred to a Sun workstation (Sun Microsystems, Mountain View, CA) for analysis. Regions defining whole brain were obtained (segmented) from all 124 contiguous slices using a semiautomated iterative morphologic technique.[8] All segmented scans were put into the orientation defined by the Montreal Neurologic Institute 305 brain average[12] using a 6-*df*

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Supported by the Alzheimer's Society (J.M.S.), Medical Research Council (N.C.F., M.N.R.), and GlaxoSmithKline (unrestricted educational grant).

Received November 15, 2004. Accepted in final form March 28, 2005.

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Table 1 *Longitudinal MR measures of global brain atrophy in established Alzheimer disease*

Study (ref.)	Year	Structure	Mean (SD) rate /y	n	Interval
5	2002	Ventricle (mL)*	8.2 mL	14	1 y
6	2003	Ventricle (mL)	5.5 ± 3.2 mL	24	5.8 y
This study	2004	Ventricle (mL)†	4.1 ± 2.3 mL	38	6 mo
			4.7 ± 2.4 mL		1 y
7*	1998	Ventricle (%)‡	14.2 ± 8.5%	24	1.9 y
5	2002	Ventricle (%)	13.8 ± 4.8%	14	1 y
4	2002	Ventricle (%)	13.0 ± 2.4%	5	2.5–7 mo
1	1997	Brain§	2.8 ± 0.9%	9	13 mo
2	2000	Brain§	2.4 ± 1.1%	15	12 mo
3	2001	Brain§	2.0 ± 0.9%	9	About 12 mo
4	2002	Brain	2.1 ± 0.5%	5	2.5–7 mo
5	2002	Brain	2.4 ± 1.2%	14	1 y
This study	2004	Brain§	2.1 ± 1.8%	38	6 mo
			2.2 ± 1.2%		1 y

Selected studies reporting annual mean (SD) volume of percentage atrophy are shown.

* Lateral ventricles only.
† Using ventricular boundary shift integral.
‡ Temporal horn of lateral ventricles only.
§ Using brain boundary shift integral.

registration. The 6-month and 1-year scans thus derived were registered to the baseline registered image using a 9-*df* registration.[13] Ventricular volumes were outlined on the baseline and two repeat images for each subject using 60% of mean brain region intensity as an upper threshold. Ventricular volumes included the lateral ventricles and temporal horn of the lateral ventricles but not the third or fourth ventricle and were outlined on all sequential brain slices encompassing these regions.

Prior to commencement of the study, an experienced rater performed ventricular outlining on 10 test scans. A second rater was taught the segmentation technique and performed a total of 30 blinded segmentations, outlining each of the test scans between two and eight times. Reliability coefficient both within and between raters was >99.9%.

Statistical analysis. For both the 6-month and the 1-year intervals, ventricular volume change and whole-brain volume change were calculated in two ways. First, change was calculated by subtracting the outlined regional volume on the repeat scan from the baseline region (whole brain) or vice versa (ventricles) and expressed as volume change (mL) per year. Second, change was calculated directly from the outlined regions using the boundary shift integral (BSI) technique. Ventricular (VBSI) and brain (BBSI)–derived whole-brain volume changes were calculated and expressed as annualized volume change (mL) from baseline. Comparisons between mean rates of atrophy at 6 months and 1 year and between rates of atrophy estimated using different techniques were made using paired *t* tests. Corresponding comparisons between variances were made using the Pitman test.

Sample size calculations. To compare the statistical power of clinical trials that use rates of ventricular expansion as the primary outcome with those that use brain atrophy, we assumed that a drug that slows the rate of brain atrophy by a certain percentage would also slow the rate of ventricular expansion by the same percentage. We used standard methods[2] to calculate sample sizes that give 90% statistical power to detect 20% reduction in atrophy rates and ventricular expansion (using two-sided significance test). Sample sizes for randomized controlled clinical trials required to achieve a particular statistical power to detect a particular proportional reduction in an outcome variable are proportional to the square of the coefficient of variation (CV) of the outcome variable in cases. The relative numbers of patients required for two different outcome variables are therefore given by the square of the ratio of the respective CVs. Ninety-five percent bootstrap CIs (bias corrected) for such relative sample sizes (using a logarithmic transform for reasons of symmetry on a relative scale) were calculated using 1,000 replicates.

Relationship between ventricular expansion and whole-brain atrophy. The percentage of the brain volume loss attributable to ventricular gain ($\Delta V/\Delta B$) was calculated for each individual at 1 year as the VBSI ventricular change (mL/y) divided by the BBSI brain volume change (mL/y). This ratio was summarized separately in cases and controls by dividing the sum of the ΔV values by the sum of the ΔB values, an approach that eliminates the potential for measurement error in ΔV and ΔB to introduce bias.[14] This is computationally equivalent to using a regression model relating ΔV to ΔB, constrained to pass through the origin and weighted by the inverse of ΔB, an approach that also yields CIs. These regression models were extended to compare $\Delta V/\Delta B$ in cases and controls and to assess whether $\Delta V/\Delta B$ was related to ventricular volume (mean of measurements at baseline and 1 year to avoid spurious correlations between measured changes and baseline values). Stata version 8 (Stata Corp., College Station, TX) was used for all analyses.

Results. *Clinical details of study subjects.* The AD and control groups were well matched for gender (AD: 23/38 women, controls: 10/19 women) and age (patients: 69.8 ± 7 years, controls: 69.3 ± 7 years). Average follow-up time for the 6-month interval was 180 ± 7 days and for the 1-year period 365 ± 14 days; these intervals were similar for both cases and controls. The AD patients had significantly lower MMSE scores than the controls (AD: 19.5 ± 4.0; controls: 29.5 ± 0.7).

Rates of whole-brain atrophy. The mean baseline brain volume was 970 mL (SD 112 mL) in cases and 1,119 mL (SD 79 mL) in controls. In cases, the mean annualized change was around 20 mL (about 2.1 to 2.2%) at both 6 months and 1 year for both segmented differences and BBSI-generated differences (table 2). These rates were around 10 to 15 mL/y greater in cases than controls over

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Table 2 *Annualized change for patients with Alzheimer disease and control subjects using a variety of techniques over intervals of 6 months and 1 year*

Interval/region and method	Mean ± SD control (n = 19) annual volume change, mL	Mean ± SD patient (n = 38) annual volume change, mL	Mean (95% CI) Patients–controls difference annual volume change, mL
6 mo (180 ± 7 d)			
Whole brain			
BBSI	6.8 ± 10.5	20.0 ± 17.7	13.2 (5.7, 20.8)
Segmented differences	9.2 ± 29.2	24.1 ± 21.5	14.9 (−0.6, 30.4)
Ventricles			
VBSI	0.8 ± 1.4	4.1 ± 2.3	3.3 (2.3, 4.3)
Segmented differences	0.8 ± 1.3	4.2 ± 2.4	3.5 (2.4, 4.5)
1 y (365 ± 14 d)			
Whole brain			
BBSI	8.1 ± 5.0	20.8 ± 11.2	12.6 (8.3, 16.9)
Segmented differences	10.9 ± 12.4	20.1 ± 12.5	9.2 (2.1, 16.3)
Ventricles			
VBSI	0.9 ± 1.0	4.7 ± 2.4	3.8 (2.9, 4.7)
Segmented differences	1.0 ± 1.1	5.0 ± 2.5	3.9 (3.0, 4.9)

BBSI = brain boundary shift integral; VBSI = ventricular boundary shift integral.

both time periods, using either technique. For both cases and controls and with both segmented differences and BBSI-generated differences, as predicted, variability in atrophy was greater at 6 months than at 1 year ($p < 0.001$ for all comparisons). In controls, between-subject variability in atrophy was markedly greater for segmented differences than for BBSI-derived changes at both 1 year and 6 months ($p < 0.001$ at both time points). In cases, there was a reduction in variability with the use of BBSI, but it was less marked than in controls and not significant at either time point.

Rates of ventricular expansion. The mean baseline ventricular volume was 52.7 mL (SD 25.5 mL) in cases and 31.7 mL (SD 22.1 mL) in controls. Mean annualized ventricular changes were around 3 to 4 mL/y greater in cases than controls for each technique at each time point ($p < 0.001$ for all comparisons). Variability at 1 year was somewhat lower than at 6 months in controls ($p = 0.04$ for

Table 3 *Numbers needed in each group for a placebo-controlled clinical trial to provide 90% power to detect a 20% reduction in outcome variable using a 5% significance level (two sided)*

Interval/outcome variable	Estimated numbers required per treatment arm	Relative trial sample size (95% CI)	
		Relative to use of BBSI at 6 mo	Relative to use of BBSI at 1 y
6 mo (180 ± 7 d)			
Whole brain			
BBSI	410	1	—
Segmented differences	419	1.02 (0.54–1.76)	—
Ventricles			
VBSI	165	0.40 (0.23–0.73)	—
Segmented differences	176	0.43 (0.26–0.76)	—
1 y (365 ± 14 d)			
Whole brain			
BBSI	154	0.37 (0.23–0.59)	1
Segmented differences	204	—	1.32 (0.72–2.28)
Ventricles			
VBSI	141	—	0.92 (0.52–1.70)
Segmented differences	135	—	0.88 (0.54–1.50)

BBSI = brain boundary shift integral; VBSI = ventricular boundary shift integral.

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VBSI, $p = 0.07$ for segmented differences), but among cases, there was no evidence of a material reduction. VBSI-derived differences were on average smaller ($p < 0.001$ in cases at 1 year) and less variable than segmented differences ($p = 0.06$ in cases at 1 year, $p = 0.02$ in cases at 6 months), but these differences in mean and SD were small in magnitude (see table 2).

Sample sizes for trials. Table 3 shows the sample size requirements for clinical trials that have 90% statistical power to detect 20% reductions in whole-brain atrophy and ventricular expansion. Table 3 also shows the ratio of the sample sizes for other outcomes relative to that using the BBSI. These ratios hold generally for any expected percentage treatment effect and any required statistical power. In comparison with a 6-month trial using BBSI as the outcome variable, switching to VBSI results in a significant reduction ($p < 0.05$) of around 60% in the necessary sample size. For example, in a 6-month placebo-controlled randomized trial that has 90% statistical power (at a two-sided 5% significance level) to detect a 20% reduction in whole-brain atrophy using the BBSI, 410 patients are required in each group; using the VBSI, only 165 patients would be required in each group to provide equivalent power.

With use of BBSI, increasing the length of follow-up to 1 year also reduces the necessary sample size by around 60% ($p < 0.05$); using the VBSI instead of the BBSI at 1 year is also associated with a reduction in trial size, but this effect was smaller and not significant. In general, sample size requirements are greater with indirect (segmented volume differences) than with direct (BBSI or VBSI) measures, but the differences are not significant.

Relationship between ventricular expansion and whole-brain atrophy. The percentage of the brain volume loss attributable to ventricular expansion ($\Delta V/\Delta B$) was higher ($p = 0.007$) for the patients (mean 22%, 95% CI 19 to 26%) than the control subjects (mean 11%, 95% CI 4 to 18%) at 1 year. In both cases ($p = 0.012$) and controls ($p = 0.049$, but no longer significant when 1 influential point was removed), there was evidence that this proportion increases with increasing ventricular volume (mean of baseline and follow-up measurements) (figure). Standardizing for ventricular volume, the difference between patients and control subjects was approximately halved in magnitude (crude difference 12% [95% CI 3 to 20%], adjusted difference 6% [95% CI −3 to 0.14%]) and was no longer significant.

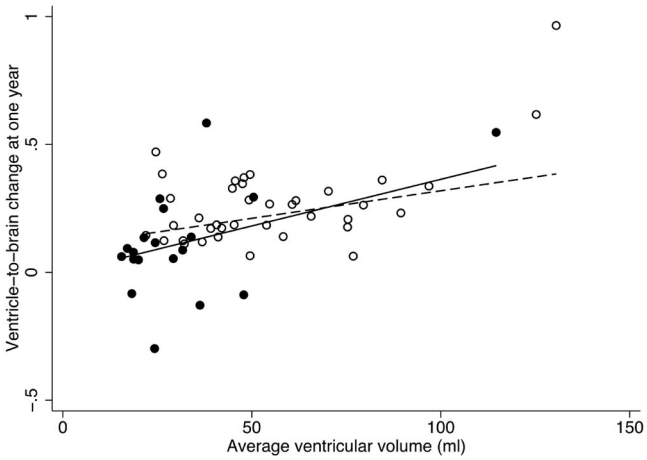

Figure. Average (baseline and 1 year) ventricular volume plotted against proportion of whole-brain atrophy attributable to ventricular expansion (ventricular/brain boundary shift integral) calculated over 1 year. Filled circles = controls; open circles = Alzheimer disease. Regression lines are shown for each group (solid = controls; dashed = cases).

Discussion. The results from this study confirm previous CT[15-17] and MRI (see table 1) studies reporting that rates of cerebral atrophy and ventricular expansion are significantly higher in AD than control cases. To date, only one published study of five patients has reported global brain atrophy rates in AD at <1 year.[4] In this larger prospective study, we demonstrate that significantly increased rates of global brain atrophy may be demonstrated in AD at intervals as short as 6 months.

The BSI has been proposed and validated as a semiautomated method for directly determining volume change from registered scans and thereby reducing measurement error.[1,8,18] In this study, we found further evidence to support these findings especially for whole-brain changes, when use of the BBSI consistently reduced measurement variability. Reflecting the very high degree of accuracy with which ventricular segmentation can be performed from registered images, there was, however, little material benefit in using VBSI over the segmented volume differences. We also showed that whereas variability in rate of change of the BBSI more than doubled as interscan interval decreased from 1 year to 6 months, there was negligible change in the variability of the VBSI with changing interscan interval. This difference again reflects the consistency with which ventricular measurement may be measured: The ventricular system is centered deep within the brain and is therefore relatively protected from changes in position within the scanner's magnetic field and thus from inhomogeneity, and the ventricle/brain boundary is a high-contrast boundary, increasing ease of segmentation. By contrast, the brain as a whole is a larger structure and is more susceptible both to inhomogeneity artifact and to edge/field-of-view effects. In this study, brain and ventricles were carefully segmented by experienced operators, and we used the BSI technique to calculate volume change occurring between serial scans based on the segmented regions. The BSI technique may be most useful in improving the accuracy of measurement in situations when the quality of segmentation is more variable. With the methodology we employed, using the BSI did not result in a reduction in operator time. Refinements of the BSI technique now allow for measurements of regional atrophy based only on segmentation of the brain region in question on the baseline scan.[19] In such cases, use of the BSI technique may result in not only increased accuracy but also considerable savings in terms of operator time.

The difference in variability of VBSI and BBSI measures over different intervals has particular significance if atrophy measures are to be used in clini-

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cal trials. Global brain atrophy has been proposed as a surrogate marker of disease progression, allowing differentiation of disease-modifying from symptomatic effects: A truly disease-modifying agent would be expected to reduce the rate of global brain atrophy toward that of normal aging.[2] Power calculations estimating patient numbers required for therapeutic trials are critically dependent on the variance of measured atrophy. The results of this study show that using the VBSI rather than the BBSI significantly reduces the estimated number of patients required in a 6-month trial (from about 410 to 165 per arm to detect 20% reduction in atrophy with 90% statistical power, at a two-sided 5% significance level). Increasing the interscan interval from 6 months to 1 year leads to a similar reduction in sample size if either the BBSI (about 152 per arm) or the VBSI (about 140 per arm) is used; these estimates are both similar to, but slightly higher than, a previously reported estimate.[2]

Over a 1-year period, a 1-mL decrease in brain volume in AD was on average accompanied by about 0.22 mL of ventricular expansion, whereas in control subjects, there was only about a 0.11-mL ventricular expansion per milliliter of whole-brain loss. This significant difference could reflect that atrophy in AD occurs more centrally than in normal aging. Although we found some evidence to suggest that a diagnosis of AD per se is associated with an alteration in the relationship of brain volume loss and ventricular expansion, we found that mean ventricular volume was the only significant independent predictor of increasing ventricular change per unit brain reduction. This finding is in keeping with a previous study in which a larger temporal horn volume at baseline was associated with a greater subsequent rate of temporal horn enlargement.[20] One possible explanation to account for these findings is that once cortical volume loss exceeds a critical amount, inward cortical movement may be restricted by external structures (e.g., dural bridging veins), resulting in relatively more ventricular change per subsequent unit of brain loss.

The findings of alterations in the relative rates of ventricular expansion and whole-brain atrophy with increasing ventricular volume (and to a lesser extent with AD per se) suggest that consistent relationships between these two measures of brain atrophy must not be assumed. It is possible that drug therapies could alter ventricular and brain volumes to different extents, as was seen in the AN1792 amyloid β-protein vaccination study.[21] Assessing alterations in the relationship of brain volume loss and ventricular expansion may provide valuable information concerning possible mechanisms of drug action.

In terms of trial sample sizes, ventricular measures appear to be superior to whole-brain measures,[18] particularly over short intervals. However, these potential advantages must be balanced against the fact that ventricular volume changes may be more likely than whole-brain measures to be influenced by factors other than neurodegeneration, such as dehydration, hydrocephalus, diuretic therapy, and alcohol.[22] Measures of whole-brain volume change might be expected to be more inherently stable and thus more biologically plausible measures of progression in AD; strategies for reducing the variance (and consequently trial samples sizes) of the brain BSI measurement, perhaps by designing trials with more than two scans, may decrease sample sizes using this technique. Further studies are required to determine the linearity of atrophy over short periods and to assess the factors (such as age or disease severity) that might impact on variability in atrophy rates, the key determinant of statistical power.

The demonstration that volume changes may be detectable in AD at intervals as short as 6 months may have particular relevance in determining pilot efficacy of disease-modifying drugs before larger and more expensive Phase III studies are embarked upon. Such approaches are clearly dependent on the time course over which therapy may be effective. In short-interval studies, combining VBSI and BBSI measurements of atrophy may not only harness the power of the former with the biologic plausibility of the latter but also allow for the possibility that drugs may alter not only the rate, but also the distribution, of atrophy in AD.

Acknowledgment

The authors thank the subjects and their caregivers for participating in the study.

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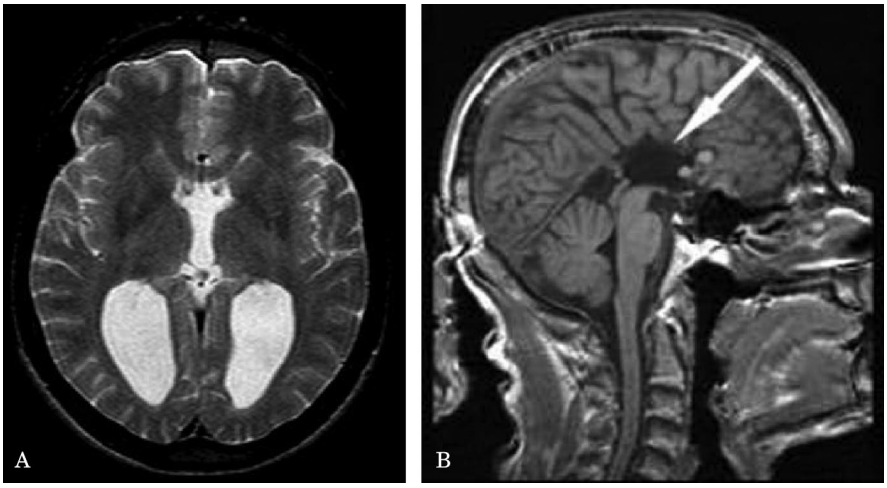

Figure. (A) Axial T2-weighted and (B) sagittal T1-weighted MRI images showing subtotal agenesis of corpus callosum with persistence of the genu. Abnormalities of medial parietal and cingulate gyri architecture as well as reduction of posterior interhemispheric callosal fibers are shown. The third ventricle is dilated with increase of interthalamic distance. There is enlargement of the posterior horns of the lateral ventricles.

Subtotal corpus callosum agenesis with recurrent hyperhidrosis-hypothermia (Shapiro syndrome)

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A 33-year-old man suffered recurrent episodes of diffuse hyperhidrosis and hypothermia (HH) lasting 2 to 3 hours (Shapiro syndrome).[1] During a prolonged episode, he was admitted for acute onset of abdominal pain and diarrhea. Pancreatitis was diagnosed. Diffuse hypotonia was the only neurologic sign. MRI showed subtotal corpus callosum agenesis with persistence of the genu (figure, A and B). Fluids and clonidine were administered. Pancreatitis was resolved and HH disappeared, recurring twice when clonidine was withdrawn. Callosal agenesis is usually associated with other brain malformations.[2] In this syndrome we found an isolated dysgenesis. A possible hypothalamic dysfunction may explain recurrent HH.

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Neurology 2005;65;124
DOI 10.1212/01.WNL.0000160423.17825.5E

This information is current as of July 11, 2005

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