Patients with nonsyndromal craniosynostosis have a recognizable cranial deformity named after the involved sutures, although descriptions based on head shape are commonly used (such as scaphocephaly, trigonocephaly, frontal synostotic plagiocephaly, brachycephaly and synostotic occipital [or posterior] plagiocephaly for sagittal, metopic, unilateral coronal, bilateral coronal, and unilateral lambdoid synostosis, respectively). Usually sporadic, nonsyndromal craniosynostosis is the most common form of craniosynostosis.

Gault and colleagues, using CT determinations of ICV and Lichtenberg's cephalometric determination of normal ICV, investigated whether craniosynostosis results in a smaller-than-normal ICV. They found that most individuals were in the normal range, although the ICVs for all craniosynostosis groups, other than for Apert syndrome, were smaller than normal. They found that the SD scores were statistically significant only if all data were pooled and patients with Apert syndrome were excluded. Posnick and colleagues measured preoperative ICVs for patients with metopic and sagittal synostosis and found that their children's preoperative ICVs were generally above the age- and sex-matched norms of Lichtenberg. Comments on that paper raised questions regarding the comparative normal data and the methods for obtaining them. Netherway and colleagues found that the ICVs in patients with nonsyndromal craniosynostosis were not smaller than those found in the Abbott–Netherway CT-determined normative data. With a larger sample size, Anderson and colleagues reported reduced ICVs for patients with metopic synostosis. In this paper, the ICVs in patients with a range of nonsyndromal craniosynostoses have been measured and statistical tests performed to determine whether significant differences exist relative to the Abbott–Netherway data on normal ICV.
Clinical Material and Methods

Patient Selection

All patients with craniosynostosis presenting at The Australian Craniofacial Unit undergo CT scanning as a part of the management protocol. Patients with nonsyndromal craniosynostosis who had no surgical intervention prior to their CT scan were selected for ICV measurement. Table 1 gives the patient numbers and age distributions for each sex and diagnosis. The two measurements for patients with bilateral lambdoid synostosis were for the same patient.

Determination of ICV

For ICV measurement, the CT slices were processed one at a time to obtain the area of intersection of the region of interest with each slice. The in-house software package Persona was used to contour (that is, outline) the bone in each slice at the specified soft-tissue/bone threshold and to edit the contours.9 Triangulation of the contours was found useful for visualization and error detection and correction. A threshold of 150 Hounsfield units was selected for determination of the bone surface for the children in our study. The ICV was calculated as the sum of the cross-sectional areas that intersected the region of interest multiplied by the slice separation (referred to as the Cavalieri estimator). A bias correction term was applied to compensate for the effects of partial voluming, depending on slice thickness and separation. This method allowed us to use our archived CT scans, which had data acquisition resolutions (slice thicknesses) ranging from 1 to 5 mm.

Comparison With Normal Intracranial Volume

The Abbott–Netherway normal curves7 were used for comparisons. These were based on Ratowsky's11 reparametrization of the three-parameter, asymptotic, regression-growth curve \( y = a \left(1 - e^{-kx - b}\right) \). The curves for each sex give the logarithm of the ICV as a function of the logarithm of the age from conception (\( y \) and \( x \) in the above equation, respectively). The use of the logarithm means that the coefficient of variation (SD/mean) was modeled as constant across the entire age range.

An ICV SD score for each patient was determined as the difference between the natural logarithm of the patient’s ICV and the sex-matched normal curve evaluated at the patient’s age, divided by the SD. The SD score variable has an expected mean of zero and a SD of unity. Two-sample t-tests between the mean SD scores and F tests between variances were performed between each patient group and the sex-matched normal group.

Results

The SD scores for the ICVs of patients with nonsyndromal craniosynostosis are shown in Fig. 1, and their descriptive statistics are given in Table 2. The ICVs of all but two individuals were within the normal range of variation, and both of these were larger than normal.

Only the group of boys with metopic synostosis (Fig. 2) had significantly smaller ICVs than normal. Of the boys with metopic synostosis older than 7 months of age, only one was above the age- and sex-matched mean. Partitioning the male metopic data into age groups younger and older than 7 months of age revealed that the younger group had normal ICVs (\( p = 0.339, 17 \) patients), whereas the older group had statistically significant smaller ICVs (\( p = 0.015, 8 \) patients).

The group of girls with metopic synostosis showed no indication of having smaller ICVs: only one patient was older than 7 months, and she had a positive SD score of 1.34. Individually, patients with sagittal synostosis span the normal range of ICV (SD score range 2.2 to 2.1). Girls with sagittal synostosis (Fig. 3) have higher than normal ICVs (\( p = 0.0002 \)), whereas those of boys are not significantly different from the normal values (\( p = 0.231 \)). This result for sex is in contrast to that reported by Netherway, et al.,8 who used a smaller population.

The boys with unilateral coronal synostosis (Fig. 4) had larger than normal ICVs (\( p = 0.001 \)). All but one had an ICV and the sex-matched normal curve evaluated at the patient’s age, divided by the SD. The SD score variable has an expected mean of zero and a SD of unity. Two-sample t-tests between the mean SD scores and F tests between variances were performed between each patient group and the sex-matched normal group.

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Fig. 1. Graph showing the SD scores for ICVs for male (M) and female (F) patients with nonsyndromal craniosynostosis: metopic (MS), sagittal (SS), unilateral coronal (UC), bilateral coronal (BC), unilateral lambdoid (UL), bilateral lambdoid (BL) and both posterior sagittal and bilateral lambdoid (MB).
ICV larger than the mean normal ICV; the exception was the oldest in the sample at 26 months. The youngest had an exceptionally large ICV, with an SD score of 3.2. On review, there was no clinical reason to exclude this patient’s data. When he was removed from the sample, the mean SD score was reduced from 1.14 to 0.94, the median score decreased from 1.28 to 1.11, and the probability value increased from 0.001 to 0.040†, thus the high value has little impact on the finding of a larger than normal ICV.

Lambdoid synostosis is rare, and both sexes are not represented in our study. Our patients with unilateral and bilateral lambdoid synostosis had unremarkable ICVs, with SD scores in the range from 0.09 to 1.02. The patient with bilateral lambdoid synostosis whom we have measured at 15 months and at 6 years showed a slight relative increase in ICV, growing from SD score 0.38 to 1.02. She has had no surgical intervention.

Of the three patients with posterior sagittal and bilateral lambdoid synostosis (sometimes referred to as Mercedes–Benz syndrome because the sutural ridging pattern resembles the well-known automobile icon), two have intracranial volumes within the normal range, whereas one of the boys has an SD score of 3.15. The F test (see the last column of Table 2) indicated that the variance for the males in this group was greater than normal. The ICV variance for the other nonsyndromal groups did not significantly differ from the normal range. The ICVs in the patients with bilateral coronal synostosis were within the normal range.

**Discussion**

In the principal studies comparing the ICVs in patients with craniosynostosis and those of a reference of normal individuals, many authors questioned the validity of the ref-
patients with metopic synostosis tended to be less than normal.

Similarly, Posnick and colleagues stated: "...we were surprised to find that our children’s preoperative intracranial volumes were generally above age- and sex-matched norms." Marsh said of Posnick and colleagues’ paper that it “...raises basic questions concerning the selection of comparative ‘normal’ data.” He concluded as follows: “...it is unlikely that the controversy regarding actual intracranial volume measurements in patients with craniosynostosis will be resolved until a normative data set has been obtained using the same methodology and technology as for analysis of the synostosis group.”

The normal data of Abbott and colleagues were based on a population of European decent who had undergone diagnostic CT scanning for conditions such as headaches, seizures, and trauma that should not have affected their ICV. Caution is always needed because of the possibility that data of this type may be biased toward underdevelopment on the basis that ill health is more likely to impede development than to enhance it. Nevertheless, no evidence has been found for such a bias in their data. The CT data were contemporaneously collected using protocols and technology similar to that used for clinical assessment of patients treated in a craniofacial surgery department. Here we have compared our ICV measurements for patients with nonsyndromal craniosynostosis with this normal population.

We found little evidence that the ICV of patients with nonsyndromal craniosynostosis is smaller than normal except for boys with metopic synostosis. Only two individuals, a boy with sagittal synostosis and a boy with metopic synostosis had SD scores less than −2. The mean for male patients with metopic synostosis tended to be less than normal (p = 0.04). This finding for metopic synostosis was reported by Anderson, et al., using the same data as reported here. Further inspection of the data revealed that it was the patients older than 7 months of age who contributed to this low ICV finding. If very young male patients with metopic synostosis indeed have normal ICVs and the older group have reduced ICVs (on average), then these findings could have implications for management of these patients. If a patient group were found to have smaller ICVs than a normal reference group, it may be that that group is simply underdeveloped in regard to the reference group rather than as a direct result of the pathological findings. Because these children as a group have normal ICVs before the age of 7 months and then have smaller ICVs on average after 7 months, an association between the pathological entities and ICV is indicated; however, the impact on brain development remains uncertain. This impact may be clarified by further cases and by longitudinal follow up.

For patients with metopic synostosis, Gault, et al., reported reduced—although not statistically significant—ICVs relative to the Lichtenberg normal group for five boys and three girls, and Posnick, et al., reported larger ICVs than the Lichtenberg group for seven boys and three girls, whereas Marsh reported ICVs for four patients within one SD of the Lichtenberg group. Our findings are more in keeping with those of Gault, et al., and of Marsh.

All patient groups with nonsyndromal craniosynostosis other than boys with metopic synostosis had positive mean SD scores, meaning that, on average, patients in our sample had larger than normal ICVs; however, this was statistically significant only for girls with sagittal synostosis and boys with unilateral coronal synostosis. Both of these groups had a sample size of 11. It is possible that a larger sample size may show that these groups do not differ from normal ones, but the evidence from this study is that the average ICV for patients in these groups is larger than normal.

For patients with sagittal synostosis, Gault, et al., reported normal ICVs relative to the Lichtenberg group for 30 boys and 16 girls, and Posnick, et al., reported larger ICVs than the Lichtenberg group for six boys and two girls, whereas Marsh reported ICVs for five patients within one SD of the Lichtenberg group. Our findings for our sagittal synostosis groups were that their ICVs are in the normal range but have a bias toward being larger than normal for girls.

It is notable that the age range for our study group of girls with sagittal synostosis is up to 5.7 months, whereas the unoperated boys in our database extend in age up to 14 years, perhaps indicating a previous preference for intervention for girls.

As stated earlier, we found that the ICV for boys with unilateral coronal synostosis tended to be larger than found in the Abbott–Netherway normal group. Gault and colleagues did not report separately for boys and girls but indicated that the ICVs were less than those of the Lichtenberg group for patients with coronal synostosis.

Differences between our findings and others (using Lichtenberg’s normal curves) can be accounted for partly by consideration of the age- and sex-dependent differences between the Lichtenberg and the Abbott–Netherway normal curves, and partly by sample differences from the relatively small sample sizes in studies on this topic. Lichtenberg...
pooled his data for boys and girls younger than 12 months of age, which would have contributed to the sex differences identified by Gault and colleagues. Much of the data for patients with nonsurgically treated craniosynostosis are for ages younger than 1 year.

Surgical intervention for craniosynostosis is undertaken to correct and prevent further distortion of the craniofacial skeleton and because of the attendant potential for constriction of brain growth. For all groups with nonsyndromal craniosynostosis, other than boys older than 7 months of age with metopic synostosis, there is no indication of ICVs being smaller than normal; in addition, two groups have a tendency to have ICVs that are larger than normal. Therefore, intervention for these nonsyndromal craniosynostoses should appropriately be focused less on ICV and more on normalizing craniofacial shape and promoting normal development.

Conclusions

No evidence was found that the ICVs in patients with nonsyndromal craniosynostosis are smaller on average than those of normal patients, except for boys with metopic synostosis. Both the groups of girls with sagittal synostosis and the boys with unilateral coronal synostosis had larger than normal ICVs. That the boys with metopic synostosis have normal ICVs and the older group have reduced ICVs (on average) may have implications for the timing of surgical intervention for these patients, although the small sample size for the older group suggests that the addition of further cases would be prudent to validate the tentative association. The indications are that surgical intervention should focus less on ICV and more on normalizing craniofacial shape and promoting normal development.

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