MR quantification of brain structures.

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AJNR Am J Neuroradiol 1993, 14 (2) 507-509
http://www.ajnr.org/content/14/2/507.citation

LETTERS

Extradural Hematomas: Surgical and Nonsurgical Treatment

We read with interest the paper, "Nonoperative Management of Acute Epidural Hematoma Diagnosed by CT: The Neuroradiologist's Role" (1). The paper focuses on the contribution of neuroradiology in providing information to neurosurgeons about which extracerebral hematomas can be treated nonsurgically. The conclusions are that favorable prognostic features can be identified (small lesion volume, minimal midline shift) as can unfavorable features (large volume, central lucent area, evidence of significant mass effect). Whereas we share these conclusions, the paper is followed by a comment from Sagher et al (2) which recommends restricting conservative management to those few cases of high convexity extradural hematomas (EDH) of an unprecise volume and to EDH detected 48 hours or more after trauma; furthermore, they consider routine conservative management of even asymptomatic EDH as "hard to justify."

The comment is not surprising. A paper published in 1985 (3) reporting 12 cases of conservatively treated EDH was followed by the comment, "This is a thought provoking and, in some ways, courageous study. The patients are the ones with courage" (4). In 1986, a paper by our group (9) was followed by a comment by Cooper which stated, "Early operative evacuation of these lesions seems to be much safer, much less expensive and more truly conservative management" (6). The reluctance to accept the possibility of nonsurgical management of EDH seems to be the same in 1992 as it was in 1985.

The availability of computed tomography (CT) scanners in the 80s and 90s produced a significant change in the population of patients harboring EDH who were admitted to neurosurgical wards. In our area, CT scanning of every minor head-injured adult patient with a skull fracture (7) allowed the detection of a large number of asymptomatic hematomas (8).

In the past these patients always existed but were submitted to a sort of "inadvertent conservative management" in peripheral hospitals. A few of them underwent clinical deterioration and were transferred (sometimes too late) to neurosurgery for treatment. Whereas EDH is the most frequent lesion if we examine a population of asymptomatic patients with skull fracture (7), they are present in only 12% to 17% (9, 10) of patients who "talk and deteriorate."

The goal is to identify the few cases at risk of deterioration and not to operate on the vast majority of EDHs that are not prone to enlarge. The pure identification of the EDH is a lifesaving procedure: the patient is transferred for observation to neurosurgery (in Europe, minor head-injured cases are kept for observation outside neurosurgery) and even if improper conservative management is instituted, clinical deterioration occurs where the patient can be treated. The time interval following trauma is, to our knowledge, the single most important factor in predicting the possible evolution of EDH towards enlargement. As suggested by Knuckey (11), patients studied within 6 hours of injury are at higher risk of deterioration. In our protocol for conservative management, we repeat a CT scan within 12 hours if the first examination was performed in the first 6 hours and within 24 hours in all the other cases. The third CT is scheduled on the fifth day and then the patient is transferred to the referring hospital where repeat studies are done on day 15 and day 30 (frequently as outpatients). With this protocol, in the last 109 consecutive cases of pure extradural hematoma, 27 were managed conservatively. In one case, the patient deteriorated between the controls and underwent immediate surgery. Mortality (regardless of clinical condition) was limited to one patient and morbidity to two patients (unpublished data).

In conclusion, we believe that the detection of hematomas in the asymptomatic phase is the major goal of neurotraumatology in the 90s. *Inadvertent conservative management* should be transformed into *intentional choice* between surgical and nonsurgical treatment. EDH can be treated safely in neurosurgery with a nonsurgical option when: 1) a suitable protocol with repeat CT studies is instituted, 2) the patient is asymptomatic (5, 8), 3) the location of the hematoma is outside the posterior fossa (3, 5), 4) there are no signs of instability such as low-density areas (1) or air bubbles (12) in the hematoma, and 5) there is no or minimal midline shift (3, 5, 8).

Most of the above-mentioned criteria are based on the CT appearance of hematomas. Collaboration between neurosurgeons and neuroradiologists in planning the nonsurgical treatment of EDH is fundamental. The time has come, in our opinion, to leave papers on conservative management of EDH to the critical opinion of the readers without the mandatory presence of a tutorial comment at the end.

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Editor's note: Duly noted.

MR Quantification of Brain Structures

Weis et al (1), in their MR study of brain structures in Down syndrome (DS), report that the cranial cavity is not significantly different between young adults with DS and control subjects. They state that "the typical brachycephalic skull form of persons with DS, which was also obvious in our subjects with DS, had no influence on the volume of the cranial cavity in comparison with that of the controls." Furthermore, they state that the smaller intracranial size reported by Schapiro et al (2) "occurred mainly because the authors used only seven CT scans for their measurements. Thus, they were not able to measure the volume of the whole cranial cavity." Finally, Weis et al report that the ratio of the brain to the cranial cavity is reduced in DS. We question these assertions for the following reasons.

The results of Weis et al showing no decrease in cranial cavity volume in those with DS (1443.2 ± 99.0 cm^3) compared with controls (1571.1 ± 231.0 cm^3) differ from early studies, which showed a smaller skull in DS subjects using measurements of head circumference (3, 4), length and width of the skull (3), and an index that expresses three-dimensional skull growth based on linear measures from skull radiographs (5). Furthermore, because brain size determines cranial capacity and because the brain of young adults with DS is smaller than that of control subjects, one might expect the cranial cavity also to be small in DS.

In the CT study by Schapiro et al (2) the total cranial volume was noted to be smaller in young adults with DS compared with healthy, age-matched male control subjects. In fact, the total cranial volume referred to the whole cranial cavity, rather than to the 7-slice section used for the remainder of the analysis. Unfortunately, this was not clear in the paper because of editing of the original data. We suggest different reasons for the discrepancy between the results of Schapiro et al and those of Weis et al.

In examining the data from the study of Weis et al, one notes that the cranial cavities of those with DS are smaller than those of control subjects, but not significantly. This lack of significance may be related to the small number of subjects studied as well as to the large coefficient of variation in their control group for intracranial volume. Unlike our study, in which the coefficient of variation (standard deviation/mean) of intracranial volume was similar in DS and in control subjects (8.4% in the DS subjects and 9.7% in the controls), the coefficient of variation for their control group was more than double that for their DS group (DS, 6.8%; controls, 14.7%), suggesting that the control group used by Weis et al was more heterogeneous. Why this increased coefficient of variation was present in the control group for cranial cavity and not for brain volume is not apparent, because the ratio of brain to cranial volume in controls is constant in the age range studied (6). In contrast to our study, which used only male control subjects, the study of Weis et al used both male and female control subjects, sex-matched to their DS group. Since postmortem (7) and quantitative CT (8) studies show that men have larger brains than women do, the inclusion of both sexes in a control group would increase the coefficient of variation. Because our preliminary statistical analysis showed no difference between male and female DS subjects, we chose to use only one sex as a control group (males) to reduce the variance in the control group. Using a male control group would probably increase the likelihood of finding a difference in intracranial and brain volume between the DS and the control group, whereas use of a female control group would produce the opposite effect. Another method of analysis might be to compare DS and control groups by sex. Alternatively, one must note that DS subjects are significantly smaller in stature than control subjects. Although a relation of head size to height has been shown (7), a height-matched control group might better answer the question of whether having DS causes one to have a proportionately smaller head.

Of interest to the appearance of Alzheimer disease in DS is the determination of whether the smaller DS brain is due to atrophy. To determine this, the ratio of brain size to cranial volume should be determined in each subject separately, to reduce the variance within groups and the influence of the heterogeneity of cranial sizes, as might be seen among sexes. In using both sexes, however, one must be cautious that there are not proportional differences in percentage brain volumes between male and female controls (8). Unlike the finding of Schapiro et al (2) with quantitative CT scanning, and of Jernigan and Bellugi (9) with quantitative MR scanning, that there was no proportional decrease in brain size, the study of Weis et al suggested that the brain is proportionately smaller in subjects with DS compared with control subjects (75.0% vs 83.6%, $P < .001$). Such a finding would imply that an atrophic process occurs in the brains with DS. However, all three groups noted no significant difference in the percent ventricular volume between DS and control subjects. The reason for the discrepancy between the results of Weis et al and those of the others is not readily apparent.

However, it should be noted that the control ratio reported by Weis et al differs from the value of 92.2% ± 1.6% (SEM) reported by Davis and Wright (6) in their study of a control population and from the value of 92% reported in the MR study of Jernigan and Bellugi (9). In addition, some of the subjects studied by Weis et al were older than 40 years, an age at which all subjects with DS show some neuropathology of Alzheimer disease and, if demented, progressive ventricular dilatation. Although the authors noted that the control subjects had no clinical symptoms, no comments were made on the cognitive profile of the subjects with DS, including whether or not dementia was absent. Previous work has shown that DS subjects over age 40 years show a universal cognitive deterioration on standardized neuropsychologic tests, more severe in demented as compared with nondemented older DS subjects (10). Dementia occurs in 40% of older DS subjects. Furthermore, both cross-sectional and longitudinal quantitative CT studies show exaggerated increases in ventricular and cerebrospinal fluid volumes in older DS subjects with clinically evident dementia (10). The inclusion of such older DS subjects in an analysis exploring the relation of mental retardation and brain structure may lead to an erroneous calculation of brain atrophy.

We do agree with the statement of Weis et al that "no significant differences in the structures of interest can be detected when the structure of interest as well as the reference structure show equivalent differences." However, we would argue that knowing whether a particular structure is relatively different from a reference structure is important information. As an example, pathologic studies suggest that the cerebellum is relatively smaller than the cerebrum in DS (11). Only through the use of a reference ratio, in this case the cerebellum/brain volume ratio, can one confirm such a thesis. In fact, Weis et al and Jerrigan and Bellugi both show that the cerebellum is not disproportionately smaller in DS.

Thus, young adults with DS have smaller than normal brains, but not disproportionately smaller than expected from their smaller stature and cranial vault. In the future, quantitative structural imaging will need larger numbers of sex-matched DS subjects and healthy control subjects, whose cognitive status has been measured, to determine the relation of brain and skull size to mental retardation in DS, and whether cerebral atrophy occurs in young DS adults before the development Alzheimer-type neuropathology.

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Reply

In response to the letter of Dr Schapiro we would like to make the following comments:

General: It is noteworthy that many researchers who apply quantitative methods ignore the proper application of stereologic methods. Stereology is a body of mathematical methods relating three-dimensional parameters defining a structure to two-dimensional measurements obtainable on sections of the structure (1). Thus, reliable and unbiased results can only be obtained using stereologic methods (2) (S. Weis and E. Wenger, unpublished data, 1992). Taking into account possible shortcomings in "know-how," one can understand why linear measurements are still in use, especially in neuroradiology.

Cranial cavity: Linear measurements are invoked to prove that the skull circumference in persons with Down syndrome (DS) is small compared with control subjects. How can one reliably extrapolate a linear measurement of skull circumference to get the volume of the skull? Schapiro mentioned that in their study "the total cranial volume referred to the whole cranial cavity, rather than the 7-slice section used for the remainder of the analysis." How can this kind of a morphometric analysis be explained? Some parameters are determined using seven sections whereas more scans are used to determine other parameters. We wonder how this kind of quantitative analysis works?

Percentages: It seems that many people are not only unaware of the reference trap quoted in our paper and the clear-cut demonstration of how one can easily fall into it, but also of how to prevent it. One statement holds: as long as one finds the expected differences, one is on the right

track. But when one does not find any difference, one is in big trouble. Therefore, conclusions should never be based on relative values but have to be supported by absolute values.

Sample size: Indeed the size of the analyzed sample was small. Although quite a number of persons with Down syndrome agreed to participate, many became frightened and anxious in front of the MR scanner and refused. We registered a dropout rate of 55% of the DS persons analyzed. Therefore it was necessary to accept a small sample size.

Coefficient of variation: It is well known that the individual differences in parameters such as body height, skull circumference, brain weight, etc, show less variation in the group of DS than in a group of normal control subjects. Thus, for comparative studies of this kind, it is more reasonable to consider the variations derived from a large population in a smaller sample (3, 4).

Male and female brains: Sex as a variable was included as a covariate in the analysis of variance. In our sample there was no difference between the two female and five male brains in both the control and the DS groups. In addition to the multivariate procedures, we also used nonparametric tests to encounter the problem of the small sample size. So, we agree that it is necessary to control statistical differences between both groups for each sex. We think it is biased to include both sexes in the DS group and one sex in the control group.

Body height, head size, and brain size: Schapiro cites reference 7 in his letter in a wrong and misleading way when speaking of "head size," since these authors entitled their paper ". . . .: relation of brain weights to body height and body weight." In our paper, we cited a study in which the correlation between brain size and body height was analyzed by using the data of more than 3,000 autopsies. This paper (from former East Germany written in German with an English abstract) is probably not known to English-speaking investigators. The above-cited authors could not find any significant correlation either for the male or the female group. Based on these data, one should question the general belief concerning the direct relationship between body height and brain size.

Ventricular size and Alzheimer disease: The statement that "all DS subjects aged more than 40 years show some kind of an Alzheimer neuropathology and, if demented, ventricular dilatation" may be in vogue but lacks a sound scientific basis. Based on our own neuropsychologic analyses of 180 subjects with DS, we reiterate that not all DS persons aged more than 40 years develop Alzheimer disease (5). Relating dementia to ventricular enlargement parallels the similar naive approach of relating schizophrenia to enlarged ventricles.

Cognitive deterioration and Alzheimer disease: We are aware of the problem of clinical signs of Alzheimer disease in adults with DS (6–8). The DS persons in our investigation showed no major signs of deterioration in cognitive profiles. Their cognitive performances were within the range of mild to moderate mental retardation. Furthermore, since childhood their clinical histories showed no decline in social or intellectual competence. An aim of our study that unfortunately could not be realized was to compare control subjects with persons with DS having "normal" cognitive profiles and with those having "low" cognitive profiles, ie, showing clinical signs of Alzheimer disease. However, those persons with DS showing "low" cognitive profile reacted violently when confronted with the MR investigation situation, showing that even the good and long-lasting social interaction between the authors and persons with DS was no help in getting these persons investigated by MR. Thus, we can refer only to a group of persons with DS showing "normal" cognitive profile.

Conclusion: The correct application of morphometric measurements to the study of CT and MR scans will give new data on the presence of brain atrophic changes and rate of progression of pathologic changes. Furthermore, these data will provide baseline information that explain more accurately the results seen in functional imaging such as SPECT, PET, and MR spectroscopy. These data, obtained in vivo, should be complemented by autopsy studies permitting the collection of data not only at the gross-anatomical level but also at the light- and electron microscopic level, thus enabling one to draw the full picture of a neuropathologic entity (2) (S. Weis and E. Wenger, unpublished data, 1992).

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Where's the Septum Pellucidum *at*?

It is out of honor and respect for my late high school Latin teacher, Mr James Murphy, that I feel compelled to comment on a grammatical error that occurred in an otherwise scholarly and interesting recent paper in this journal (1). In particular, I am referring to the misuse of the term "cavum septum pellucidum" which occurs repeatedly throughout this article. The proper grammatical structure for this phrase should be "cavum septi pellucidi," which translates as "cavity of the septum pellucidum."

In Latin *cavum* and *septum* function as nouns while *pellucidum* is an adjective which modifies *septum.* Expressing the concept "cavity *of* the septum pellucidum" requires that *septum* and *pellucidum* be placed in the genitive form, namely "septi pellucidi." "Cavum septi pellucidi" is thus not only grammatically correct, but is also the official Nomina Anatomica designation for this entity which appears in most textbooks and medical dictionaries. It is also the form used in the titles of every reference quoted by the authors of the present paper.

Synonyms for cavum septi pellucidi include: cavity of the septum pellucidum, camera septi pellucidi, Duncan's ventricle, fifth ventricle, rhomboid sinus, sinus rhomboideus cerebri, ventricle of Arantius, ventricle of Sylvius, and Vieussen's ventricle (2). Incidentally, the proper term for the space of Verga is "cavum vergae," while the cavity of the velum interpositum should be called the "cavum veli interpositi."

I realize 3 years of high school Latin doesn't make me a classical scholar (although only 2 years of fellowship does qualify me to be a neuroradiologist!) Nevertheless, I am quite confident that I still remember how to decline these Latin words properly, and feel that *AJNR*, as the world's leading journal for neuroradiology, should insist both upon the "King's English" and "Caesar's Latin" in all of its articles. Mr Murphy wouldn't have had it any other way.

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Conclusions Questioned

I read with interest the article by Degreef et al (1) regarding abnormalities of the septum pellucidum in first-episode schizophrenic patients. However, their demonstration of a case of "partial agenesis of the corpus callosum" (Fig. 3) appears incorrect. The embryology of the corpus callosum reveals an anterior to posterior sequence of development, with the exception of the rostrum. This concept is important in differentiating a dysgenetic corpus callosum from one that is secondarily injured; a small or absent genu or body is almost certainly the result of a secondary destructive process when the splenium is intact (2). Figure 3A clearly shows a normal splenium, making the diagnosis of partial agenesis unlikely. Moreover, when the corpus callosum does not form, the cingulate gyri remain everted and the cingulate sulcus remains unformed (2). Figure 3B shows normal inversion of the cingulate gyri, also making the diagnosis of partial agenesis unlikely.

I question the conclusion that the authors reach in the abstract. Even if the case of partial callosal agenesis had been correct, the presence of a single example in 62 patients would hardly qualify as an "increased prevalence of partial callosal agenesis in schizophrenics" (regardless if other studies have supported this finding). In summary, their paper presents 62 cases of first-episode schizophrenia in which there are no examples of callosal dysgenesis and one case of a secondary destructive callosal lesion.

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Editor's note: These letters were referred to Dr Lantos and his colleagues. Their reply follows.

Reply

We have read Dr Friedman's letter with interest and reviewed our case in light of the points raised. The development of the corpus callosum is quite complex. The first major embryologic event involves thickening of the dorsal end of the primitive lamina terminalis (lamina reuniens) at about 6 to 8 weeks of gestational age. This structure evolves into the commissural plate, through which the anterior commissure, corpus callosum, and hippocampal commissure eventually migrate. The process starts with the anterior commissure at about 10 weeks, followed by the hippocampal commissure at approximately 11 weeks, and the corpus callosum at about 12 weeks (1).

The cellular/molecular mechanisms of formation of the major commissural tracts have not been completely elucidated. Postulated mechanisms include fusion of the medial hemispheric walls to form the commissural plate, followed by penetration of the commissural plate by glial cells to

form primitive interhemispheric bridges called "glial slings (2)." However, the cytokinetic factors involved in this process have not been identified.

It is true that the case cited in our paper does not represent the usual partial agenesis of the corpus callosum, wherein the posterior aspect of this structure is frequently absent. However, there was no clinical evidence of trauma (surgical or otherwise), previous inflammatory disease, previous infarction, or other potential acquired causes for the manifest absence of the midportion of the corpus callosum in this individual. Furthermore, it would be difficult to imagine any acquired destructive process involving so circumscribed a region of the corpus callosum and which, in addition, exquisitely spared all nearby structures.

Therefore, while we do not have pathologic proof, we believe that a developmental anomaly of the corpus callosum best explains the MR appearance. Although much is unknown about the ultrastructural mechanisms of the development of the corpus callosum, one pathogenetic explanation might be that two separate corpora callosae may have developed, for unknown cellular and molecular reasons, in analogy with the separate development of anterior commissure, posterior commissure, and corpus callosum under normal circumstances. Another possibility is that there was excessive axonal elimination in the midportion of the corpus callosum, resulting in the gap seen on MR. The existence of axonal elimination is a well-documented phenomenon in experimental models (3, 4), but its role in human brain development is still incompletely understood.

For the above reasons, we ask for Dr Friedman's and other *AJNR* readers' forbearance in our interpretation of the MR findings in the case under discussion. It is possible that unusual cases such as these may spur further consideration of matters of human brain development by our colleagues in neurobiology and neuropathology. Beyond this, we agree that the statement about increased prevalence of partial agenesis in schizophrenic patients may be too broad, based as it was on only one observation. However, the development of the corpus callosum has been the subject of some attention in the literature (5, 6).

There is not much we can say in response to Dr Elster's letter except the following. Dr Elster, in scholarly fashion, points out our incorrect use of the term "cavum septum pellucidum." We defer to his superior classical knowledge and can only say in response, NOSTRA CULPA. (We hope that's right!)

Please let us know if you would like any additional information.

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Editor's note: The letter from Dr Friedman was also referred to Dr A. James Barkovich for his comments. They follow.

Reply

The article by Degreef et al (1) brings up a number of interesting points. The search for significance of the cavum septi pellucidi is a long one, marked by many disputes. Is it a normal, incidental variant or a sign of abnormal embryogenesis? The article by Degreef et al supports the former. However, as the authors point out, cavae are by no means rare in the "normal" population; the significance of this finding in an individual patient, therefore, is unclear.

Regarding the callosal abnormality in the single patient in their series, I must agree with Dr Friedman's comments. The abnormality is certainly not "partial callosal agenesis." The MR appearance of partial callosal agenesis (callosal hypogenesis) has been described several times (2–4). Almost invariably, the corpus callosum begins to form above the region of the foramen of Monro at the posterior portion of the genu, followed by the formation of the body, splenium, and, finally, rostrum. Inversion of the cingulate gyri, which is present in the patient illustrated in Figure 3 of the article by Degreef et al does not typically occur in the portions of the brain where the corpus is unformed. Very exceptionally, the middle portion of the corpus may be absent in the presence of an apparently normal splenium (5) or genu and splenium (6). However, these very rare variants have only been described in the setting of holoprosencephaly or a variant thereof. In the case reported by Degreef et al, the interhemispheric fissure appears to have formed completely and, therefore, does not fit into the spectrum of holoprosencephaly with callosal dysgenesis.

What, then, does the focal narrowing of the corpus in this schizophrenic patient represent? First, it is important to remember that more than 20% of neurologically normal patients have thinning of the corpus callosum at the junction of the posterior body and splenium (7), the exact

location of the thinning in the patient reported by Degreef et al. Thus, it is entirely possible that their patient represents an extreme of a normal variant. The cause of this variant may be mild focal ischemia of the corpus or its precursors at the intervascular boundary zone between the anterior and posterior circulations. Focal callosal thinning can also be seen as a result of focally diminished hemispheric white matter in association with schizencephalies and with focal degenerative or destructive disorders of white matter (4); however, neither condition was apparent in this case. Disorders in the development of cortical layers 3, 4, and 5 can also affect callosal development as callosal fibers originate in neurons of layers 3 and 5, and terminate in layers 4 and 3 (2). However, the authors give no suggestion of cortical abnormalities in their patient.

To summarize, presence of a cavum septi pellucidi in an adult is an unusual, but by no means rare, finding. Degreef et al have presented evidence that the incidence of persistent cavae is higher in schizophrenics than in the general population. However, I must agree with Dr Friedman's objection to the authors' conclusion that there exists an "increased prevalence of . . . partial callosal agenesis in schizophrenics" based upon the evidence in their paper.

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Editor's note: I have taken the liberty of also forwarding Dr Elster's letter to Dr James Scatliff, author of an article that recently appeared in AJNR (Scatliff JH, Clark JK. How the brain got its names and numbers. *AJNR: Am J Neuroradiol* 1992;13:241–248). Dr Scatliff's reply follows.

Reply

Thanks ever so much for the chance to see Dr Elster's letter. It was very kind of you to think of me as a classicist. In my next life I am going to try very hard to be an archeologist and write novels about it!

With my limited Latin (only 2 years at Evanston Township High School) I think Allen is right. I looked in Gray's Anatomy, and the cavum is indeed called "the cavum septi pellucidi." I am not sure about the genitive form. If "septi" connotes two septums, that certainly would seem to be right for the cavum which does sit, of course, between two leaves of the septum pellucidum. If my reading is correct, I believe that is what Gray's Anatomy says.

I discussed Dr Elster's concern with Jonathan Clark who, is studying classics here at UNC. As I started saying "cavum septum pellucidum," I could see his eyebrows go up. I could tell that something northwest of his septum pellucidum was struggling with what I had just said. I told him about the "cave" in the septum. He said that it definitely should be in the possessive case and that cavum septi pellucidi is correct. I think Dr Elster's letter is terrific. As you may know, the Elsters have triplets. I am sure that he has plurality on his mind, ie, "septi and tripletti."

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