

## Clinical progression of incidental tomographic findings in paranasal sinuses of asymptomatic individuals: cohort study

Severino A. de Araújo-Neto,<sup>1</sup> Emílio C. E. Baracat<sup>2</sup>

### Abstract

**Objective:** To determine whether the presence of opacification in the paranasal sinuses of children and adolescents without rhinosinusitis implies an increased risk of later development of upper respiratory tract symptoms.

**Methods:** This was a prospective study of a cohort of patients aged 0 to 18 years who underwent computerized tomography (CT) scans for indications unrelated to rhinosinusitis. Sinus opacification was evaluated using an opacification/development ratio score. The patients' clinical progression was followed up using a questionnaire for 1 month after the scans.

**Results:** Fifty-six percent (56%) of the 106 patients enrolled in the study had opacity, the majority due to mucosal thickening. Intense opacification was defined as "suspected" (score  $\geq 15$ ) and patients in this subset had a greater risk of developing symptoms during follow-up (odds ratio = 2.74; 95%CI 1.10-6.83) compared to those with no findings or discrete findings.

**Conclusions:** Intense incidental sinus opacity on CT indicates a risk of future development of a clinical respiratory condition.

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### Introduction

Symptomatic inflammation of the mucosal lining of the paranasal sinuses (PS), which is known as rhinosinusitis (RS), is highly prevalent and can be classified as acute, recurrent or chronic.<sup>1</sup> Acute RS (ARS) is one of the five most common indications for prescribing antibiotics<sup>2</sup> and because of this it is necessary to distinguish it from other conditions in order to avoid unnecessary use of these medications.

Diagnosis of RS is primarily clinical.<sup>1</sup> Simple X-rays offer very low accuracy and nowadays computerized tomography (CT) is the gold standard.<sup>3,4</sup> It is unusual to use a CT scan to diagnose ARS, but its indication for chronic RS cases

(CRS), which often involve obstructions such as nasal polyps and anatomic abnormalities, is well-established. If intraorbital or intracranial complications are suspected then a CT scan or a magnetic resonance image (MRI) with contrast is indicated.<sup>1,2,4,5</sup>

Mucosal thickening, fluid levels and total opacification of PS are all findings typical of RS,<sup>6</sup> but can also be observed in patients with colds, influenza, rhinitis and allergic asthma at rates that vary from 33 to 88% of patients.<sup>7-11</sup> Even in people free from any respiratory disease whatsoever, these are often incidental findings.<sup>12-18</sup>

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1. Doutor, Faculdade de Ciências Médicas, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil. Professor adjunto I, Universidade Federal da Paraíba (UFPB) e Faculdade de Ciências Médicas da Paraíba (FCM-PB), João Pessoa, PB, Brazil.
  2. Doutor. Professor associado, Departamento de Pediatria, Faculdade de Ciências Médicas, UNICAMP, Campinas, SP, Brazil.

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Many authors have stated that opacity has no clinical significance when there are no symptoms of RS.<sup>12,13,19</sup> However, others claim that significant abnormalities merit clinical follow-up.<sup>12</sup>

The objective of this study is to investigate whether sinus abnormalities found in CT scans of asymptomatic children and adolescents are predictive of clinical progression to rhinosinusitis.

### Methodology

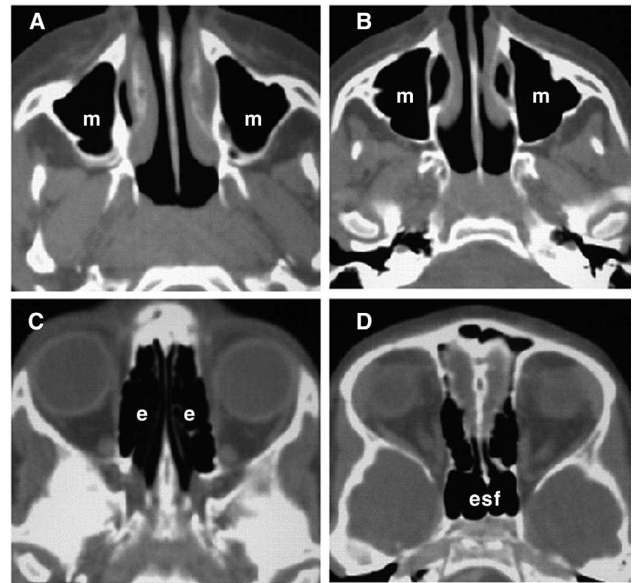
This was a longitudinal cohort study. Informed consent was obtained from parents or guardians and the project was approved by the Research Ethics Committees at the teaching institutions involved.

Consecutive patients aged 0 to 18 years were recruited at a radiology department after referral for CT scans of the head for reasons other than RS. Patients were excluded if there was a suspicion of RS or clinical status suggestive of RS, if they had CRS or had been diagnosed with ARS less than 2 months previously, if they had suffered a recent head trauma, had had radiotherapy of the head or neck, or if they had cystic fibrosis or gastroesophageal reflux disease. Patients were also excluded if their scans did not show the paranasal sinuses in their entirety or if they were lost to clinical follow-up.

A clinical score at admission (S5adm) was calculated for each patient by administering the S5 questionnaire,<sup>20</sup> which grades five RS signs and symptoms on a scale from 0 to 3 points (head or face pain, daytime coughing, nighttime coughing, obstruction and runny nose). The final score varies from zero to three and is calculated by summing the sub-scores and dividing by five. The questionnaire's authors<sup>20</sup> defined S5 scores > 1 as positive for RS and this was adopted as the cutoff point for excluding patients from the sample.

The technique used for head CT scans was the standard method used at the department, consisting of axial slices parallel to the orbitomeatal line, varying from 2 to 5 mm, at the posterior fossa, and from 5 to 10 mm, in the supratentorial region, depending on the size of the patient. Additionally, the scans performed on the study sample included two additional, more caudal, slices at the level of the maxillary sinuses (Figure 1), at an angle that did not bisect the plane of the eyes. Other sinuses were already covered by the slices for the head scan. The following helical CT machines were used: Tomoscan SR-4000 (Philips, Eindhoven, Holland), Helicat Flash (Elsint Company, Israel) and X-Vision (Toshiba, Tokyo, Japan). The images were saved as bitmap files with levels of 0 to 400 HU and widths of 1,000 to 2,000 HU.

The CT scans were interpreted independently by two different radiologists with a minimum of 4 years' experience



**Figure 1** - Axial computerized tomography slices. A and B show the maxillary sinuses (m); C and D are the head slices that show the ethmoid (e), frontal (f) and sphenoid (esf.) sinuses

in the specialty, blind to the S5 scores. They indicated their opinions of the following items for each sinus: a) presence of opacification; b) degree of opacification; and c) type of opacification (thickening, cyst/polyp, total or fluid level opacification). Disagreements were resolved by consensus.

The intensity of opacification was quantified by the opacification/development ratio (ODR), which has been validated previously.<sup>21</sup> Each sinus was scored as follows for the opacification component: a) 0 (zero) if normal or not yet developed; b) 1 (one) if < 2/3 of the area is opaque; c) 2 (two): if  $\geq 2/3$  of the area is opaque; and d) 3 (three) if opacification is total. The opacification score is the numerator of the ODR. For the development component, sinuses that are present score 3 (three) and absent sinuses score 0 (zero). The sum of the development scores is the denominator of the ODR. The percentage of opacity is therefore calculated as follows:

$$\text{ODR} = (\text{total opacification}/\text{total development}) \times 100.$$

The result, which is in the range of zero to one, is multiplied by 100 to give an estimate of the percentage of the area of the PS that is opaque.<sup>18,21</sup> Patients were divided into two groups: "low probability" of opacification (ODR < 15) and "suspected" opacification (ODR  $\geq 15$ ). The cutoff point chosen was that which offered the best accuracy for RS.<sup>21</sup>

Opacity types were classified as total opacification and fluid level combined in one category or cysts/polyps and thickening in another. The extent of opacification was

classified as “one sinus affected” vs. “2 or more” vs. “all sinuses affected.”

The clinical follow-up score (S5fol) was recalculated weekly for 4 weeks after the scan by telephone interview using the same S5 questionnaire. The outcome was defined as negative if the patient scored S5fol  $\leq 1$  and positive if S5fol was greater 1 after any of the interviews.

SPSS version 13.0 was used to calculate statistics to a significance level of 5% ( $p < 0.05$ ). The tests applied were as follows: the Mann-Whitney (MW) test and Kruskal-Wallis ANOVA were used to compare the means of two, or more, independent samples respectively; the Dunnett multiple comparisons test was used to supplement tests of the means of more than three independent samples in order to determine which was responsible for differences; the chi-square test or Fisher’s exact test were used for associations between categorical variables; Pearson’s coefficient and Spearman’s  $r$  were used to test for correlations between quantitative variables; odds ratios (OR) were used to study the cohort and significance was defined as when the 95% confidence interval (95%CI) does not pass through 1.

## Results

A total of 129 patients were scanned. Twenty-three of these cases were excluded; five because of imaging artifacts or because not all sinuses were shown and the other 18 because they were lost to follow-up. Fifty-seven (57) of the remaining 106 patients were female (53.8%). Age varied from 5 months to 18 years (mean = 6.8 years; standard deviation [SD] = 4.4 years). The most common indications for CT scans were epilepsy/convulsions (24.7%), delayed neuropsychomotor development (19.8%) and headaches (14.8%).

The maxillary and ethmoid sinuses were developed in all patients. The sphenoid sinus was developed in 77 (72.6%) and the frontal sinus in 33 patients (31.1%). Fifty-nine patients (55.7%) had some type of abnormal finding, most often in the maxillary sinuses ( $n = 46$ ; 43.4%), followed by the ethmoid ( $n = 31$ ; 29.2%) sphenoid (14/77; 18.2%), and frontal sinuses (1/33, 3.0%). The ODR scores varied from 0 to 83 (mean = 12.7; SD = 19.2). Seventy point seven percent ( $n = 75$ , 70.7%) of the sample had an ODR indicating low probability of opacification (ODR < 15) and 29.3% ( $n = 31$ ) had suspected ODR. Mucosal thickening alone was present in 72.9% of cases ( $n = 43/59$ ). Cysts/polyps and total opacification were both present in seven patients (11.9%), and fluid levels were observed in two patients (3.4%).

Opacification was most intense in the under-3 age group, according to mean ODR scores, with a progressive reduction in the succeeding age groups (Table 1). Eighteen of the 69 patients who responded to the question about allergies were positive (26.1%). There were no significant

**Table 1** - Means, deviations and ranges of opacification/development ratio by age group in a sample of patients given facial CT scans

Age group	n	Mean	SD	Range	Post hoc*
< 3 years	22	27.8	26.60	0-83	x
3 to 9 years	50	9.6	14.72	0-75	y
> 9 years	34	7.4	14.19	0-72	z

SD = standard deviation.

ANOVA:  $p = 0.003$ .

\* The Dunnett test indicates that the youngest age group (x) is different ( $p < 0.05$ ) from the other two (y and z), which, in turn, are not different from each other.

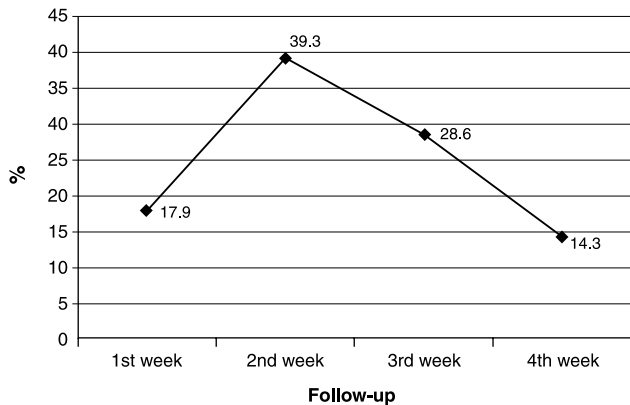
differences between patients with allergies and those free from allergies in terms of mean ODR ( $p = 0.247$ ).

Anesthesia was required during the CT scan for 41 of the 106 patients (38.7%). Anesthesia use was determined by age, being used for 90.9% of patients less than 3 years old, for 36.0% of the 3-9 year-olds and for 8.8% of the over nines. A comparison of mean ODR scores indicated a significant difference between patients who were anesthetized (mean ODR = 18.8) and those who were not anesthetized (mean ODR = 8.8,  $p = 0.004$ ).

In order to isolate the variables age and anesthesia statistically, the sample was divided into the subset that did not receive anesthesia ( $n = 65$ ) from the population who did receive anesthesia ( $n = 41$ ). When the means of the ODR scores were compared, the statistical difference between age groups were maintained in the total sample, but not in the no anesthesia group ( $p = 0.330$  and  $p = 0.026$ , respectively).

Mean S5adm was 0.41 (SD = 0.32). There was no correlation between the S5adm (0 to 1) and ODR (0 to 100) scales (Spearman  $r = 0.077$ ;  $p = 0.434$ ). There was also no difference in mean S5adm between low probability and suspected ODR ( $p = 0.467$ ). With regard to age, mean S5adm was greater in the 3 to 9 years group in relation to the other two ( $\leq 3$  years and  $> 9$  years, ANOVA:  $p = 0.013$ ). Age was also analyzed by splitting patients under five ( $n = 49$ ) from those over 5 years old ( $n = 57$ ), but there was no difference in S5adm ( $p = 0.629$ ). Mean S5adm was greater among allergic patients ( $p = 0.032$ ).

One hundred and six of the 101 patients responded to at least two follow-up questionnaires and two were already positive in the first week of follow-up. Three patients were lost to follow-up after a single interview and had not had a positive outcome, so it was decided to exclude them from subsequent analyses, which were therefore restricted to 103 patients. The outcome was positive in 28 patients (27.2%), with greatest incidence in the second week ( $n = 11$ ; 39.3%) (Figure 2).



**Figure 2** - Distribution of percentages of positive outcomes (n = 28) by clinical follow-up week

The odds ratio for the likelihood of a member of the group with suspected ODR (ODR ≥ 15) having a positive outcome was 2.74 with relation to the low probability group (Table 2). There was no increase in the risk of a positive outcome related to opacification of any specific sinus, to type of abnormality (fluid level/total opacification vs. polyps/thickening), to extent of involvement (in two categories: one sinus vs. two or more sinuses) or related to asymmetrical involvement.

**Table 2** - Clinical outcome by “suspected” opacification/development ratio (≥ 15) for patients followed-up for 4 weeks

	Negative outcome		Positive outcome		Total n
	n	%	n	%	
ODR < 15	57	79.2	15	20.8	72
ODR ≥ 15	18	58.1	13	41.9	31
Total	75	72.8	28	27.2	103

ODR = opacification/development ratio.  
Odds ratio for ODR ≥ 15 against ODR < 15 = 2.74 (95%CI 1.10-6.83);  
chi-square = 4.875; p = 0.027.

When the variable age was re-categorized into two subsets, under fives and over fives, a tendency was observed towards a positive relationship with a positive outcome, but without statistical significance (OR = 2.32; 95%CI 0.95-5.63; p = 0.06) and the same was true of patients given anesthesia (OR = 2.31; 95%CI 0.95-5.58; p = 0.061). The presence of rhinitis/asthma determined an increased risk of a positive outcome (OR = 3.56; 95%CI 1.09-11.54).

**Discussion**

Sinus opacification is often detected in individuals with respiratory conditions other than RS. Kristo et al.<sup>7</sup> studied children with upper airway infections (UAI) using MRI and found opacity in 88%. Gwaltney et al.<sup>11</sup> observed an elevated rate of abnormal CT findings in adults with the common cold (up to 87% of maxillary sinuses). Kovalhuk et al.<sup>8</sup> studied children with asthma and allergic rhinitis using CT and found opacification in 20%. Abnormal sinus findings may also be purely incidental. Havas et al. studied 666 CT scans of the heads of adults and found abnormalities in 42% of them<sup>13</sup>. Sinus opacity was present in 41% of CT scans of the temporal and orbital bones of patients aged less than 18 years who were studied by Lesserson et al.<sup>12</sup> Manning et al. studied children and adolescents using CT and MRI of the head and found abnormalities in the PS of 55%.<sup>19</sup> A recent study by Hill et al.<sup>17</sup> reported elevated figures, with opacity in around 80% of asymptomatic children and adolescents.

Sinus abnormalities were observed in 55.7% of the patients in the present study, which is discretely higher than the majority of studies. In 73% of these cases, mucosal thickening was the only finding, while total opacification of a cavity and fluid level affected a minority. This predominance of discrete opacity in patients who do not have RS is the rule in published literature,<sup>12,13,17,19,22</sup> as are the predominance of opacification of the maxillary (43%) and ethmoid (29%) sinuses and diffuse and bilateral opacification that were observed here.<sup>13</sup>

Patients younger than 3 had significantly greater prevalence and intensity of opacification than the older patients, which has also been shown in earlier studies.<sup>16,23</sup> However, the effect of anesthesia on opacification that was observed here, and has not been mentioned in prior studies, may have introduced bias into the relationship and must be investigated in greater depth in future research.

The findings reported here demand that a certain degree of opacification be admitted in the radiological definition of a “normal” sinus. According to Wald,<sup>24</sup> radiological diagnostic criteria for RS should be limited to mucosal thickening of at least 4 mm, total opacification or fluid level. The least specific of these criteria is mucosal thickening.<sup>25,26</sup> Bhattacharia and Fried used the Lund and Mackay score (LMS) for measuring opacification and established that a cutoff of ≥ 4, which they called “high probability” of RS, offered the greatest diagnostic accuracy.<sup>22</sup> An earlier study established the correlation that LMS ≥ 4 corresponds to ODR ≥ 15 (here defined as “suspected” ODR).<sup>21</sup> However, in the sample studied here, 29% of the patients, none of whom had RS, had a “suspected” ODR score, indicating a relatively high rate of false-positive results using this cutoff point and emphasizing the low specificity of tomography opacification for diagnosing RS.

In practice, radiologists should not make a diagnosis of RS without knowledge of the clinical picture. When patients are free from symptoms, opacification intensity of ODR < 15, LMS of < 4 or mucosal thickening of < 4 mm are very unlikely to be evidence of RS.

In cases where clinical diagnosis is not clear cut and radiological findings of opacity confuse the picture even further, cultures of material collected from the sinus by direct puncture or nasal video endoscopy can definitively rule out a diagnosis of RS.<sup>1,26</sup> However, these procedures are neither routine nor practical. Even if the opacity proves to be sterile, the suspicion still remains as to whether it is present because of physiological imbalances of drainage or aeration of the cavities and might yet facilitate proliferation of bacteria in the near future. This is the reason why the objective of this study was focused on the question of possible risk of clinical progression and was not restricted to criteria for interpreting what is normal and what is abnormal on a CT scan of the PS.

During clinical follow-up, 27% of the patients developed symptoms (positive outcome). Patients with ODR  $\geq$  15 (suspected) had a significantly higher chance of the outcome (OR = 2.74) when compared with those whose tomography findings were classed as low probability.

Two studies have investigated the behavior of incidental PS findings over time, but they only described imaging status and did not correlate it with patients' clinical progress. Maly & Sundgren<sup>27</sup> conducted a retrospective analysis of adults who had been scanned twice with MRI for neurological reasons with a minimum interval of 4 months and found that in 90% of the patients the findings were either stable or improved at the second scan. In another study, children with short-duration respiratory symptoms (< 10 days) were scanned with MRI and 43% had positive findings. 2 weeks later a control MRI showed significant attenuation of sinus abnormalities, irrespective of whether symptoms had improved.<sup>7</sup>

As has been seen, allergic patients were at greater risk of the positive outcome, which may mirror exacerbations of their allergic conditions during follow-up. It is improbable that the allergies introduced any bias to the association between suspected ODR and the positive outcome, since no relationship was detected between allergy and ODR scores. Young age (< 5 years) and anesthesia also exhibited a tendency, although without significance, towards an increased risk of the positive outcome. The association with young age may be the result of the high incidence of inflammatory respiratory conditions among these children. The explanation for the role of anesthesia is not so clear cut. It is possible that statistical significance would have been achieved with a larger sample. Since both these factors also exhibited a relationship with higher ODR scores, the possibility that the risk of the positive outcome conferred by suspected ODR is merely the effect of a bias of association

with young age and/or anesthesia cannot be ruled out. This possible interference should be investigated in greater depth in future studies.

The study design imposed certain limitations of a methodological nature on this research. Some of the inclusion/exclusion criteria restricted the sample size and increased the time taken to complete the study, specifically, head trauma, previous history of RS and the prospective triage and exclusion of symptomatic patients. The exclusions due to lost follow-up also contributed. Furthermore, the extremely low expected monthly incidence of RS in an asymptomatic population meant that a patient who reached S5fol > 1 at any point would be withdrawn from follow-up irrespective of the duration of symptoms. Therefore, the "positive outcome" in this study indicates clinical deterioration, but not necessarily RS. Therefore, if the evidence reported here is to serve as a foundation for recommendations of clinical follow-up of asymptomatic children and adolescents with intense opacification, it is also necessary to assess the benefits of those recommendations, whether for observation or preventative measures.

We preferred the ODR to the well-established LMS because the latter is of limited application with children since its scoring system does not take any account of absent sinuses.<sup>21,28</sup> As the ODR is based on the proportion of the total developed PS area that is opaque, it is less susceptible to interference from peculiarities of the growth and development of children and adolescents.

Summing up, more than half of this sample of asymptomatic children and adolescents had abnormal PS CT results, with a predominance of discrete, incidental areas of opacity. The presence of more intense opacification (suspected ODR) at the time of admission increased the risk of developing upper respiratory signs and symptoms during the month following the first scan.

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## Correspondence:

Severino A. de Araújo Neto  
 Rua Maria Helena Rocha, 113, apto. 1102  
 CEP 58036-823 – João Pessoa, PB - Brazil  
 Tel.: +55 (83) 3421.2985; +55 (83) 9946 9915  
 Fax: +55 (83) 3421.2985  
 E-mail: severinoaires@hotmail.com