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Improvement of psychiatric symptoms in youth following resolution of sinusitis

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ABSTRACT

Introduction: Accumulating evidence supports a role for inflammation in psychiatric illness, and the onset or exacerbation of psychiatric symptoms may follow non-CNS infections. Here, we provide the first detailed description of obsessive-compulsive and related psychiatric symptoms arising concurrently with sinusitis.

Methods: We reviewed the charts of 150 consecutive patients evaluated in our Pediatric Acute-onset Neuropsychiatric Syndromes clinic for documented sinusitis as defined by the American Academy of Pediatrics guidelines. Sinusitis treatments, sinonasal imaging, and neuropsychiatric symptoms before, during, and after sinusitis onset were noted. Patients were included in the final review if they had a clear diagnosis of isolated sinusitis (without concurrent illness and/or immunodeficiency), and were evaluated during an episode of sinusitis.

Results: 10/150 (6.6%) patients had isolated sinusitis at the time of their neuropsychiatric deterioration. Eight patients received antibiotics to treat sinusitis, three of whom also received sinus surgery. Neuropsychiatric symptoms improved in all eight patients concurrent with resolution of sinusitis per parent report and clinician assessment. One patient did not follow through with recommended sinus surgery or antibiotics and her psychiatric symptoms persisted. One patient was lost to follow-up.

Conclusions: Improvement of psychiatric symptoms correlated with resolution of sinus disease in this retrospective study. Identification, treatment, and resolution of underlying infections, including sinusitis, may have the potential to change the trajectory of some neuropsychiatric illnesses. Randomized clinical trials are needed.

1. Introduction

A growing body of literature supports a link between inflammation and psychiatric symptoms [1–5]. Concurrent inflammatory disease and psychiatric symptoms have been described in conditions including neuropsychiatric systemic lupus erythematosus [6], schizophrenia [7], acute disseminated encephalomyelitis (ADEM) [8], Behcet's [9], anti-NMDA-receptor encephalitis [10], pediatric autoimmune neuropsychiatric disorder associated with group A streptococcus (GAS) [11,12], and toxoplasmosis [13]. To our knowledge, no one has yet reported neuropsychiatric changes with isolated sinusitis.

Research criteria for a condition labeled "Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)" were created to study a group of children who have an abrupt, dramatic onset of obsessive compulsive (OC) symptoms and/or eating restriction accompanied by an equally abrupt onset of at least two co-morbid neuropsychiatric symptoms, which may include anxiety, emotional lability, depression, irritability, aggression, oppositionality, deterioration in school performance, behavioral (developmental) regression, sensory amplification, movement abnormalities, sleep disturbance,

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and urinary frequency [14,15]. The Stanford PANS program was created to research etiology and treatment for this disorder and conducts an interdisciplinary clinic designed to evaluate and treat youth with suspected PANS. Although the clinic focuses on evaluating and treating acute-onset cases, it follows a small subset of patients who presented with unclear or sub-acute onsets of PANS-like symptoms, since, over time, many of these patients' clinical conditions deteriorate acutely in subsequent relapses. The mechanism by which PANS develops is unknown and is likely multifactorial.

Children suffer an estimated six to eight viral upper respiratory infections per year. Up to 13% of these infections can be complicated by bacterial rhinosinusitis [16,17]. In children with common variable immunodeficiency (CVID), sinusitis is one of the most common infectious presentations [18]. In 2015, we reported that 11% of patients seen in the Stanford PANS clinic noted presence of sinusitis within either three weeks prior to or during the development of the first PANS symptoms [19]. To date, no one has described patients' course of neuropsychiatric illness before, during, and after sinusitis.

Here we report ten cases of patients whose escalation in psychiatric symptoms coincided with sinus disease.

2. Methods

The Stanford Panel on Human Subjects Institutional Review Board approved this retrospective study.

We reviewed the medical and psychiatric records of 150 patients who presented to the multidisciplinary PANS clinic between September 2010 and August 2015. Each patient underwent a comprehensive neuropsychiatric and medical evaluation, and this data was incorporated into patients' medical records. Data extracted from the medical record included: demographic data, the presence or absence of neuropsychiatric symptoms, and the presence or absence of symptoms consistent with acute bacterial rhinosinusitis or chronic sinusitis. Patients with a diagnosis of acute, subacute, recurrent acute, chronic, or acute superimposed on chronic bacterial rhinosinusitis based on American Academy of Pediatrics (AAP) clinical practice guidelines (Table 1) [16,20], and who met criteria for a diagnosis of PANS [14,15], or who otherwise met PANS criteria but had a subacute onset, were included for further review.

Patients for whom a comprehensive neuropsychiatric evaluation was not available or for whom a diagnosis of sinusitis was unclear were excluded from the study (Fig. 1). Patients who presented with an additional concurrent illness and/or immunodeficiency were also excluded. These patients were excluded because the effect of the interaction between sinusitis, the concurrent illness, and its treatment (such as immunomodulatory therapy to treat arthritis or intravenous immunoglobulins (IVIG) to treat underlying immunodeficiency) on the psychiatric symptoms could not be determined. A detailed description of these patients can be found in Table A1 (Appendix A). Signs of immunodeficiency were defined as leukopenia or diagnosed CVID based on significantly decreased levels of immunoglobulin G and immunoglobulin A or immunoglobulin M in addition to a poor antibody response to vaccination [21].

Sinonasal imaging (computed tomography [CT], magnetic resonance imaging [MRI]) ordered as part of routine clinical care was obtained for included patients when available. A board certified pediatric otolaryngologist re-reviewed all images for the presence or absence of sinonasal abnormalities.

We then evaluated all patients with a neuropsychiatric deterioration and concurrent sinusitis to describe the relationship between the course of PANS and sinusitis.

3. Results

3.1. Patient characteristics

Of the 150 children who presented to the PANS clinic during the study period, 70 patients (47%) had mention of sinus disease in their medical record. Of these, 41 patients were excluded because their sinusitis resolved prior to being seen in our clinic. Six patients were excluded for an unclear diagnosis of sinusitis, and 13 patients

Table 1
Diagnostic criteria used to identify patients with bacterial sinusitis.

Sinusitis symptoms:
- Purulent cloudy or colored nasal discharge
- Nasal obstruction reported as congestion, blockage, or stuffiness
- Facial pain/pressure/fullness involving the anterior face, periorbital region, or manifested as a localized or diffuse headache

Types of sinusitis	Diagnostic criteria/associated symptoms
Acute sinusitis [20, 22] (Duration: >10 days and <30 days)	• Purulent nasal drainage and/or daytime cough that persists for >10 days with no improvement OR • Worsening or new nasal discharge, daytime cough, or fever within 10 days after an initial improvement OR • Severe onset with concomitant fever of at least 102.2°F and purulent nasal discharge for at least three consecutive days
Subacute sinusitis [16, 22] (Duration: 30–60 days)	• Mild to moderate and often intermittent nasal discharge of any quantity and/or cough that is often worse at night • May have low grade periodic fever
Recurrent acute sinusitis [16, 22] (Duration: <30 days and separated by at least 10 days without sinusitis symptoms)	• 3 episodes of acute bacterial sinusitis in 6 months OR • 4 episodes of acute bacterial sinusitis in 12 months
Chronic sinusitis [16, 22, 29] (Duration: >90 days)	At least two of the following symptoms for >90 days: • Mucopurulent nasal drainage • Persistent residual respiratory symptoms such as cough, rhinorrhea, and nasal obstruction • Decreased sense of smell • Polyps • Purulent mucus or edema in the middle meatus or ethmoid region • Radiographic imaging shows inflammation of paranasal sinuses
Acute superimposed on chronic sinusitis [16]	• Development of new respiratory symptoms on top of residual respiratory symptoms AND • Treatment with antibiotics results in resolution of new symptoms but underlying residual symptoms remain

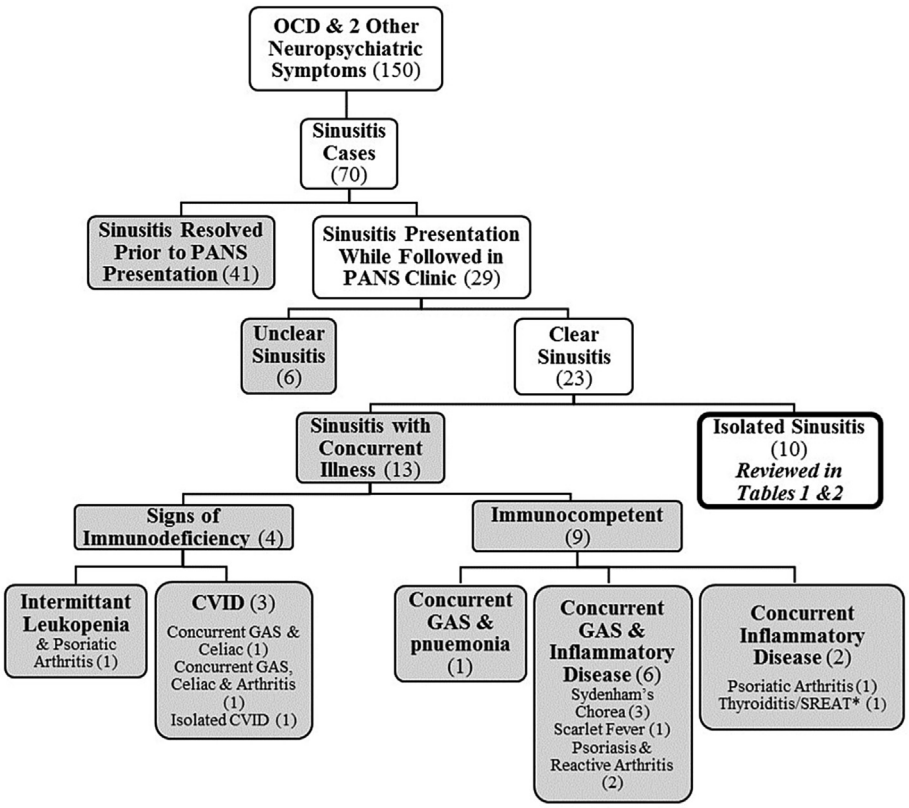

Fig. 1. Breakdown of patients excluded from review because their sinusitis resolved prior to their being seen in PANS Clinic, their diagnosis of sinusitis was unclear, or they presented with a concurrent other illness. *SREAT = Steroid Responsive Encephalitis associated with Thyroiditis.

were excluded because they presented with an additional concurrent illness and/or signs of immunodeficiency (Fig. 1 and Appendix A).

The remaining ten patients had isolated sinusitis without other concurrent infections or inflammatory diseases, and met criteria for sinusitis at the time of initial presentation of psychiatric symptoms or flare in psychiatric symptoms after a stable mental health trajectory. These ten patients ranged in ages 6–17 years old. Six were male and four were female. These ten patients are presented in Tables 2 and 3. All ten patients had severe OC symptoms as part of their clinical presentation and experienced serious disruption in their psychosocial health and school performance. Five were not able to attend school for periods of time (patients 3, 4, 6, 8, & 9). Two patients with isolated sinusitis (patients 3 & 8) required psychiatric hospitalizations, mental health services from the state, and extensive school services. Aside from minor residual symptoms, six of the seven patients who ultimately experienced resolution of their sinus symptoms and psychiatric symptoms were able to return to, or nearly to, their neuropsychiatric baseline and service needs were decreased. In contrast, patient 5, who did not follow through with recommendations to have sinusitis treated, had ongoing sinus and psychiatric symptoms at her 20-month follow-up in conjunction with other disabling psychiatric and physical symptoms.

3.2. Imaging findings

Four patients (patients 4, 5, 8, & 9) underwent imaging (CT or MRI) due to concerns for anatomic abnormalities contributing to sinusitis and/or evaluation of other organic brain issues. Upon review, all four patients had confirmed paranasal sinus abnormalities consistent with acute or chronic disease. For the remaining patients, their high neuropsychiatric impairment rendered imaging unfeasible.

3.3. Sinus surgery

Surgery was recommended by a community otolaryngologist for four patients and three followed through with sinus surgery (patients 4, 8, & 9). Indications for sinus surgery included chronic maxillary (patients 4, 5, & 8), ethmoid (patients 5 & 8), and/or sphenoid (patient 5) sinusitis and/or abnormal sinus anatomy (patients 8 & 9). Review of the surgical reports revealed chronic maxillary (patient 4 & 8), sphenoid (patient 9), and/or ethmoid sinusitis (patient 8 & 9). Maxillary mucoceles and a benign sphenoid sinus cyst were removed from patients 4 and 9, respectively. Sinus cultures were obtained during surgery for one patient (patient 4). This patient's culture found methicillin-resistant *Staphylococcus aureus* (MRSA) sinusitis resistant to all penicillins, all cephalosporins (except anti-MRSA cephalosporins), and beta-lactam inhibitor combinations. The three patients who went through with recommended surgeries also completed a recommended antibiotic course. All three experienced improvement of psychiatric symptoms following surgery. The fourth patient (patient 5) refused sinus surgery and did not complete her prescribed antibiotics regimen.

3.4. Antibiotics

All patients were prescribed standard treatment for acute bacterial sinusitis (amoxicillin/clavulanic acid) per AAP guidelines [22]. Among patients with isolated sinusitis, five received an alternative

Table 2
Characteristics of patient at presentation of neuropsychiatric symptoms & isolated sinusitis.

#	Pre-existing neuropsychiatric symptoms	Sinusitis type	New onset or dramatic escalation of symptoms during sinusitis	
			Psychiatric/cognitive symptoms	Physical symptoms
1	Sensory & motor abnormalities/tics.	Acute	Acute onset: OC symptoms, anxiety, emotional lability, irritability, behavioral regression, attention difficulties, deterioration in school performance.	Sensory abnormalities.
2	Anxiety, sensory & fine motor abnormalities, sleep disturbances *(parent report).*	Recurrent	Acute onset: Severe OC symptoms, anxiety, emotional lability, irrational behaviors, attention difficulties, deterioration in school performance.	Sleep disturbance, joint pain.
3	OC symptoms, anxiety, panic episodes, emotional lability, irritability/ aggression, attention difficulties, motoric hyperactivity, light sensitivity (*all mild per parent report).*	Acute	Acute onset: escalation of OC symptoms, emotional lability, increased irritability, personality change, deterioration in school performance, motoric hyperactivity.	Simple and complex tics, piano playing fingers, dystonia, truncal instability, sleep disturbance, fatigue, sound sensitivity, abdominal pain, constipation.
4	Mood/emotional issues, sensory abnormalities.	Chronic	Acute onset: OC symptoms, anxiety, panic episodes.	Piano-playing finger movements on standing Romberg, milkmaid grip, stress dystonia, truncal weakness and instability, sleep disturbance, enuresis, fatigue, joint pain.
5	None.	Chronic	Acute onset: OC symptoms, emotional lability, depression, irritability, cognitive changes, sensory abnormalities.	Tics, fatigue, joint pain, back pain.
6	None.	Acute	Acute onset: mild OC symptoms, emotional lability, irritability, behavioral regression.	Tics, sleep disturbance, migraines, foot pain, dizziness, sensory abnormalities.
7	Fine & gross motor abnormalities.	Acute superimposed on Chronic	Subacute onset: OC symptoms, anxiety, emotional lability, depression, irritability, cognitive changes.	Sleep disturbance, back pain, diffuse tenderness, pain amplification.
8	Mood issues, irritability, sensory abnormalities.	Chronic	Subacute onset: anxiety, emotional lability, depression, irritability, aggression.	Simple and complex tics, truncal instability, sleep disturbance.
9	None.	Chronic	Acute onset: OC symptoms, mild anxiety, mild irritability, mild cognitive changes.	Neck and body pain.
10	Anxiety, learning disabilities, fine motor abnormalities, speech delay.	Chronic	Subacute onset: OC symptoms, restrictive food intake, anxiety, emotional lability, depression, aggression, behavioral regression, cognitive changes, deterioration in school performance.	Piano-playing finger movements on standing Romberg, simple and complex tics, tongue fasciculation, sleep disturbance, urinary frequency widespread pain, abdominal pain, numbness, shooting electrical pains, sensory abnormalities.

antibiotic due to parent or physician concerns for compliance with a twice daily medication or a history of failed treatment with amoxicillin/clavulanic acid, specifically: clarithromycin (n = 1), clindamycin (n = 2), azithromycin (n = 2). One patient (patient 4) switched to sulfamethoxazole/trimethoprim after MRSA was found in his sinuses during surgery.

One patient (patient 6) was lost to follow-up, and another (patient 5) did not complete her antibiotics regimen or her recommended sinus surgery, as mentioned above. Her sinus symptoms and psychiatric symptoms including depression, anxiety, and OC symptoms persisted at her 20-month follow-up.

Overall, ten of our patients (10/150, 6.6%) presented with isolated sinusitis (no other illness or immunodeficiency) concurrent with their neuropsychiatric deterioration. Eight of these ten patients followed through with prescribed treatment and returned to our clinic for follow-up; of these, seven experienced complete resolution of their sinusitis without need for other treatments. The eighth patient, who was treated with both antibiotics and prednisone, experienced incomplete resolution of sinusitis and subsequent recrudesce of sinus disease. All eight patients experienced improvement in neuropsychiatric symptoms concurrent with resolution or improvement of sinusitis. Three patients experienced recrudesce of sinus symptoms and concurrent recrudescence of neuropsychiatric symptoms. One patient had recrudescence of neuropsychiatric symptoms following GAS exposure, suggesting that his constellation of neuropsychiatric symptoms may wax and wane with a variety of inflammatory illnesses.

4. Discussion

Sinusitis is a common infection in the general pediatric population [16]; however, there are few reported associations between sinusitis and neuropsychiatric deteriorations. The children in our case series may represent a group who are vulnerable to psychiatric exacerbations for reasons we do not understand. Their sinusitis could represent a non-specific trigger that “tips the balance” into having these overt psychiatric symptoms. Alternatively,

Table 3
Course of PANS illness, sinusitis, & treatment.

#	Neuropsychiatric symptoms after resolution of sinusitis	Time, sinus treatment to max improvement	Course of sinusitis and neuropsychiatric symptoms
1	Resolved: all symptoms (OC symptoms, anxiety, emotional lability, irritability, behavioral regression, attention difficulties, deterioration in school performance, sensory abnormalities).	3 weeks	Improvement sustained for two weeks after completion of amoxicillin/clavulanic acid course. Deterioration after antibiotics were stopped. Amoxicillin/clavulanic acid restarted with corresponding psychiatric symptom improvement, which was sustained during and several weeks after treatment with antibiotics. Mild flare in psychiatric symptoms at GAS exposure.
2	Improved: most symptoms (severe OC symptoms, emotional lability, irrational behaviors, attention difficulties, deterioration in school performance). Residual: anxiety.	Within 10 days[a]	Improvement sustained for 4 months, contracted another sinus infection, OC symptoms and attention difficulties returned. All symptoms improved within 10 days on amoxicillin/clavulanic acid, over the next four years the patient had three more neuropsychiatric flares with sinus infections that improved with antibiotics.
3	Improved: mood, aggression, sensory abnormalities. Residual: OC symptoms, anxiety, emotional lability, irritability, deterioration in school performance, tics.	10 days	Improvement sustained, currently 4 months.
4	Improved: OC symptoms, anxiety, panic episodes. Residual: fatigue, photosensitivity, intermittent joint pain.	Within 15 weeks	OC symptoms, anxiety and panic episodes improved while on antibiotics and prednisone, then resolved following sinus surgery and course of sulfamethoxazole/trimethoprim. Sinus symptoms recurred 8 months later with concurrent escalation of body pain and generalized fatigue. All symptoms improved after restarting sulfamethoxazole/trimethoprim and prednisone.
5	N/A (Sinusitis did not resolve.).	N/A	All symptoms persisted: OC symptoms, emotional lability, depression, irritability, cognitive changes, motor tics, sensory abnormalities.
6	N/A (Lost to follow-up.)	N/A	N/A
7	Improved: OC symptoms, anxiety, mood, irritability, attention difficulties, cognitive changes, pain, sleep disturbance.	Within 4 months[a]	Improvement sustained for 4 months, deteriorated when completed course of clindamycin, clindamycin restarted, improved mood and anxiety within 6 weeks but some sinus symptoms persisted, deteriorated 2 months later concurrent with resurgence of sinus symptoms, on allergist's recommendation removed tree nuts from diet. Sinus symptoms, anxiety, emotional lability, and depression improved, 4 months later sinus symptoms and neuropsychiatric symptoms returned. Received sinus surgery, IVIG, and anti-psychotic medication.
8	Improved: emotional lability, depression, irritability, tics, sleep disturbance, body pain, fatigue.	8 months	Gradual improvement for 8 months, improvement sustained, currently at 16 months post-operation.
9	Resolved: OC symptoms, cognitive issues, pain. Residual: mild anxiety and mild irritability.	Within 6 weeks[a]	Improvement sustained, currently at 27 months.
10	Improved: OC symptoms, anxiety, depression, aggression, behavioral regression, cognitive changes, sleep disturbance. Resolved: tics, pain, tongue fasciculation.	24–48 h	Slowly deteriorated, then switched to antibiotics to azithromycin, gradually improved, improvement sustained.

[a] Interval between appointments.

characteristics of the immune response or location of inflammation within the sinonasal anatomy may uniquely contribute to neuropsychiatric deteriorations. Indeed, new evidence from a mouse model suggests that antigen-specific Th17 cells generated within the nasal-associated lymphoid tissue can migrate along olfactory tracts past the cribiform plate and into the brain to promote blood-brain barrier breakdown, microglial activation, and changes in synaptic physiology [23].

In this study, we describe the clinical course of ten patients with sinusitis coinciding with a neuropsychiatric deterioration. Additional physical symptoms consistent with central nervous system (CNS) dysfunction were also present frequently (e.g. tics, dystonia, truncal instability/hypotonia, tongue fasciculations, pain, sensory amplification, sleep disturbance [Table 2, third column]). Patients who subsequently experienced resolution of their sinus disease also had significant concurrent improvement or resolution of their neuropsychiatric and physical symptoms (Table 3), suggesting a potential pathophysiologic relationship.

Prior research has demonstrated an association between acute-onset OC symptoms and GAS infections [11,12]. Transient behavior regressions with infections have been described in patients with developmental delay [24] and in normal healthy children with GAS [25]. Interestingly, a previous case series reported onset of anorexia nervosa and OC symptoms in the setting of GAS and sinusitis with improvement in the psychiatric symptoms following resolution of these infections [26]. Similarly, in our case study, neuropsychiatric deterorations were also reported in patients with GAS and concurrent sinusitis (see Appendix A, patients 11–17, 21, & 22). While only the minority of patients presenting to our PANS clinic had isolated sinusitis coincident with neuropsychiatric deterioration (10/150, 6.6%), this small group of patients may provide insight into a potential inflammatory trigger worthy of further investigation.

All patients with sinusitis in our clinic were prescribed antibiotics, per AAP recommendations [22]. However, it is unknown whether patients' sinusitis would have resolved organically in the absence of antibiotics. Prior randomized, placebo-controlled studies examining the efficacy of antibiotics as treatment for sinusitis in children have described conflicting results [17,27,28]. Randomized control trials will be necessary to determine whether sinus directed therapies improve the trajectory of neuropsychiatric

illnesses.

Our experience also indicates that future studies of neuropsychiatric disorders should track sinusitis closely, along with other potential infectious triggers and common complications of upper resipiratory infections in children. Culturing the sinuses of patients who present with sinusitis concurrent with neuropsychiatric deteriorations may provide insight into specific organisms that may correlate with these deteriorations. This approach may be especially useful given that the treatment of sinusitis was relatively safe, rapid, and low cost as compared to treatment of refractory psychiatric disease.

A limitation of this study is that we may be underestimating the total number of neuropsychiatric deteriorations that were coincident with sinusitis in our patient population for three reasons. First, we chose to describe only the small fraction of patients who presented to our clinic with *isolated* sinusitis. Second, we only included cases of *active* sinusitis at the time of neuropsychiatric deterioration, but a large portion (47%) of patients in our clinic reported a past history of sinus symptoms. We were unable to assess neuropsychiatric deteriorations occurring alongside sinusitis prior to presentation to our clinic or confirm a diagnosis of sinusitis when patients presented to other providers with neuropsychiatric deteriorations, and thus, these cases were excluded. Third, we excluded 13 patients that had other concurrent illnesses and/or immunodeficiency because the effects of sinusitis could not be isolated from the effects of the concurrent illness and treatments (i.e. IVIG and other anti-inflammatory treatments). Interestingly, of these 13 patients, 10 experienced resolution of sinus symptoms, and of these 10, nine experienced improvement in psychiatric symptoms coincident with resolution of sinus symptoms (see Appendix A, patients 13–15, 17, 18, & 20–23).

Another limitation is that specific evaluation for symptoms of sinusitis was not routinely done during the first year of our multidisciplinary clinic, limiting our sample size. Furthermore, children's psychiatric symptoms can be so overwhelming for families and providers, such that physical signs and symptoms of sinusitis may not always be appreciated.

5. Conclusion

Accumulating evidence suggests that inflammation [3–5] or infection [2,23] originating outside the CNS can impact neuropsychiatric health. Our findings extend this literature and offer the intriguing, but preliminary possibility that the identification, treatment, and resolution of underlying infections, including sinusitis (sinus inflammation), can improve the trajectory of some neuropsychiatric illnesses. Observations in our patient population suggest that clinicians should consider sinusitis among potential triggers when evaluating patients with neuropsychiatric deteriorations and recommend future research to further study the relationship between sinonasal disease and neuropsychiatric deteriorations.

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Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ijporl.2016.10.034.

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