Increase in pediatric pseudotumor cerebri syndrome emergency department visits, inpatient admissions, and surgeries during the COVID-19 pandemic

Running title: Pediatric pseudotumor cerebri admissions during COVID-19 pandemic

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Abstract

Background: Pediatric pseudotumor cerebri syndrome (PTCS) is a vision-threatening condition that is associated with female sex and obesity in pubertal and post-pubertal children. It is unknown whether the increase in childhood obesity during the COVID-19 pandemic has impacted the rates and characteristics of pediatric PTCS.

Methods: We conducted a retrospective study of children evaluated for PTCS (inpatient or emergency department) at our children’s hospital before (March 19, 2015 to March 19, 2020) and during (March 20, 2020 to February 20, 2021) the pandemic. We compared the monthly number of inpatient and emergency department encounters for pediatric PTCS before and during the pandemic. Additionally, anthropometric and ophthalmologic characteristics of children evaluated for pediatric PTCS before and during the pandemic were compared.

Results: A total of 36 encounters in the 5 years before the pandemic and 26 encounters in the 11 months during the pandemic were identified. The median monthly number of encounters for pediatric PTCS was significantly higher during the pandemic compared to the 5 years prior to the pandemic (2 vs. 0, p=0.0021). Compared to pre-pandemic patients, children evaluated during the pandemic were older (median age 16 vs. 14 years, p=0.02), with higher rates of obesity (85% vs. 66%, p=0.05) and lower likelihood of reporting white race (4% vs. 31%, p=0.02). Pandemic patients had worse presenting visual acuity (median logMAR 0.14 vs. 0.05, p=0.05) and were more likely to have fulminant presentation (23% vs. 6%, p=0.04) and require surgical intervention (23% vs. 6%, p=0.04).

Conclusions: At our children’s hospital, the rate of inpatient admissions and emergency department visits for pediatric PTCS increased during the pandemic. The severity of disease and frequency of surgical treatment also increased. Racial and ethnic minorities appear to be
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disproportionately affected. These changes may be related to increasing rates of childhood obesity during the pandemic.
Pediatric pseudotumor cerebri syndrome (PTCS) is a rare disorder, with an estimated annual incidence of 0.6 to 0.9 per 100,000. This condition is characterized by elevated intracranial pressure with normal neuroimaging (other than signs of increased intracranial pressure) and normal cerebrospinal fluid (CSF) composition. Primary PTCS is also known as idiopathic intracranial hypertension (IIH). The incidence of pediatric PTCS increases with age, female sex, and obesity; the latter two are considered significant risk factors in pubertal and post-pubertal, but not pre-pubertal, children.

Since the onset of the COVID-19 pandemic, child obesity rates have risen. Given the association between obesity and PTCS in older children, we sought to determine whether rates of PTCS increased at our children’s hospital since the onset of the pandemic. We used the state-mandated stay-at-home order on March 19, 2020 as the initial date of the pandemic because we were particularly interested in the impact of this lockdown on pediatric PTCS cases, and because there were few (52) cases of COVID-19 recognized in our county prior to this date. We specifically evaluated inpatient admissions and emergency department visits because consistent anthropometric data were obtained during these visits.

Methods

This study was approved by the local institutional review board (IRB) and adhered to the tenets of the Declaration of Helsinki and the US Health Insurance Portability and Accountability Act of 1996. We searched the electronic medical record for all children (18 years or younger) with inpatient or emergency department encounters at our hospital with a diagnosis of pseudotumor
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cerebri (International Classification of Disease [ICD]-9 code 348.2 and ICD-10
code G93.2) between March 19, 2015 and February 20, 2021. Encounters
dated on or prior to March 19, 2020 were considered pre-pandemic, and
later encounters were considered to take place during the pandemic.
Charts were reviewed to confirm diagnosis of definite PTCS, based on the 2013
revised criteria.11 Patients who met criteria only for probable or suggested PTCS
were excluded. Patients were also excluded if they did not undergo
neuroimaging or lumbar puncture, or otherwise did not meet diagnostic
criteria. Encounters for patients previously diagnosed with PTCS were
included if they had objective signs of an exacerbation, including
papilledema and/or elevated opening pressure on lumbar puncture.
Although all included patients underwent lumbar puncture with opening
pressure measurement at diagnosis, some patients previously diagnosed
with PTCS did not undergo repeat lumbar puncture if PTCS exacerbation
was confirmed by ophthalmologic examination showing recurrent
papilledema. Repeated encounters for the same exacerbation were
excluded. Both primary and secondary PTCS cases were included.

The following data were recorded: age, sex, race and ethnicity, height, weight,
body mass index (BMI), secondary cause of PTCS if applicable, neuroimaging
findings, lumbar puncture opening pressure, SARS-CoV-2 test results, and
ophthalmologic exam and test results including visual field tests and optical
coherence tomography [OCT] of the retinal nerve fiber layer [RNFL].
Treatments recommended (including surgeries) were also noted. We additionally
recorded whether patients were considered to have “fulminant” PTCS, which was
diagnosed in patients with acute symptoms and rapidly progressive vision loss
(typically headaches less than two weeks and vision loss less than one week).12
Best-corrected visual acuity was assessed using Snellen letters except for one four-year old child, who was tested using crowded Allen figures. Visual acuity was converted to logMAR and averaged between the two eyes (i.e. one measurement per encounter) for statistical analysis. Due to age, cooperation, poor vision, and in some cases lack of equipment availability when patients were assessed after hours, the type of visual field testing that could be performed was highly variable (automated, kinetic, or confrontation only). Therefore, we could not perform statistical analyses on visual field indices (e.g. mean deviation) and considered visual field to be a binary variable (normal or abnormal). Visual fields were deemed abnormal if any defect other than an enlarged blind spot was identified in either eye. One patient (pre-pandemic) had retinopathy due to vitamin A deficiency and was excluded from analysis of visual acuity and visual field defects.

BMI values were converted to age- and sex-normalized z-scores, based on Centers for Disease Control and Prevention (CDC) growth charts published in 2000. An extended BMI z-score was calculated in children whose BMI was at or above the 95th percentile, because standard z-scores are inaccurate in very obese children. BMI scores were available in all patients except for one child who presented before the pandemic who did not have a recorded height.

We did not have information on Tanner staging, and therefore used age as a surrogate for pubertal status, as in prior publications. Age less than 11 years was considered pre-pubertal.

Data were collected and statistical analyses were conducted in Microsoft Excel version 16.30 (Microsoft Corporation, Redmond, WA), GraphPad Prism version 9.0.2 (GraphPad Software, San Diego, CA), and Stata statistical software (StataCorp LLC, College Station, TX).
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Demographic, anthropometric, and clinical characteristics were compared between encounters before and after March 19, 2020. The Kolmogorov-Smirnov test was used to assess normality of continuous variables. If distributions were normal, an unpaired t-test was used for comparison. The Mann-Whitney test was used to compare non-normally distributed (skewed) continuous variables. The chi square test (Fisher’s exact test if any cells had a value less than 5) was used to compare categorical variables. P-values less than 0.05 were considered significant.

Results

We identified 36 encounters between March 19, 2015 and March 19, 2020 (pre-pandemic) and 26 encounters between March 20, 2020 and February 19, 2021 (during pandemic) meeting inclusion criteria for this study. The distribution of encounters, by month, is shown in Figure 1. The monthly number of emergency department and inpatient admissions for pediatric PTCS was significantly higher during the pandemic (median 2 vs. 0, p=0.0021).

The demographic, anthropometric, and clinical characteristics of children seen for PTCS before and during the pandemic are shown in Table 1. Children seen during the pandemic were more likely to be post-pubertal (though not reaching statistical significance) and significantly older (median 16 vs. 14 years, p=0.02) with higher BMI z-scores (2.7 vs. 2.0, p=0.02). The rate of obesity increased from 66% before the pandemic to 85% during the pandemic (p=0.05). Race and ethnicity differed significantly between groups, with fewer non-Hispanic whites (4% vs. 31%) and more Hispanic patients (77% vs. 39%) seen during the pandemic (p=0.02). Sex and
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location of the encounter (emergency department or inpatient admission) did not differ between groups.

The proportion of patients with secondary causes of PTCS also did not differ between groups. The medications and diagnoses associated with secondary PTCS included minocycline (4), steroid taper (3), growth hormone (2), polycystic ovarian syndrome (2), levofloxacin (1), and Graves’ disease (1). Only one patient with secondary PTCS (who presented during the pandemic) had a fulminant presentation and required surgical intervention; this patient was taking minocycline.

Patients seen during the pandemic were more likely to have a fulminant presentation (23% vs. 6%, p=0.04) and worse presenting visual acuity (median logMAR 0.14 vs. 0.05, p=0.05), with higher likelihood of requiring surgical intervention (23% vs. 6%, p=0.04). All eight patients with fulminant PTCS (two pre-pandemic and six during pandemic) underwent optic nerve sheath fenestrations. One patient later had a lumbo-peritoneal shunt placed due to persistent headaches and intolerance of acetazolamide; this was considered one surgical patient although two procedures were performed. The characteristics of the eight patients with fulminant PTCS are presented in Table 2. All children with fulminant PTCS were female, pubertal or post-pubertal, and overweight or obese, with a median BMI of 40. There was a greater proportion of Black children in the group with fulminant presentation (25%) compared to the total cohort of children (pre-pandemic and during pandemic) with PTCS included in this study (8%).
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Lumbar punctures were performed in 83% and 70% of encounters before and during the pandemic, respectively (p=0.19). There was no significant difference between groups in the lumbar puncture opening pressure (median 42 cm H₂O pre-pandemic vs. 48 cm H₂O during pandemic, p=0.22).

Visual fields were evaluated by confrontation, Goldmann, and Humphrey visual field tests in 43%, 11%, and 46% of patients before the pandemic, and 46%, 8%, and 46% of patients during the pandemic, respectively. There was no significant difference between groups in types of visual field testing performed (p=0.88) or the proportion of patients with a visual field defect other than enlarged blind spot (31% pre-pandemic vs. 54% during pandemic, p=0.07). Supplemental Table 1 lists the types of visual field defects other than enlarged blind spots that were identified by Humphrey, Goldmann, and confrontational visual field testing.

Optic nerve OCT was performed in 39% of patients before and 69% of patients during the pandemic (p=0.02). Upon review of the OCT reports, significant inaccuracies in the segmentation of the RNFL were noted, particularly in patients with severe optic disc edema. Due to inconsistencies in data acquisition and quality, we did not perform statistical analyses on OCT RNFL measurements.

We attempted to compare the severity of papilledema between groups using Frisen grading. After reviewing the charts and fundus photographs, if available, we were only able to ascertain Frisen grade in 10 of 36 (26%) of patients before and 9 of 26 (35%) of patients during the pandemic (p=0.56). Therefore, we did not perform statistical analyses on papilledema severity.
Conclusions

This study demonstrates a significant increase in the number of emergency department visits and inpatient admissions for pediatric PTCS after the statewide stay-at-home order triggered by the COVID-19 pandemic on March 19, 2020, as compared to the preceding five years. Additionally, there were significant differences in the characteristics of patients presenting during the pandemic – these children were older and more obese, with more severe disease and a higher rate of surgical intervention required. The burden of this increased PTCS morbidity during the pandemic has been largely borne by minorities, as the proportion of patients reporting white race decreased from 31% before the pandemic to 4% during the pandemic. Black children were particularly likely to experience severe PTCS; 25% of children with fulminant presentation requiring surgery were Black, compared to 8% of the total cohort.

The pathophysiology of PTCS is complex and likely differs in children who are pre-pubertal compared to older children. In pre-pubertal children, the sex distribution is equal, and obesity is not a significant contributing factor. However, in children who have begun or completed puberty, female sex and obesity are important risk factors. In a prospective national cohort study in the United Kingdom, the relative risk of PTCS in obese girls between 12-15 years of age was 26.2, when compared to normal weight girls of the same age. The authors found that 82% of the incidence of PTCS in children between the ages of 12-15 years was attributed to obesity. Similarly, an epidemiologic study conducted in southern California found that the adjusted odds ratio for PTCS diagnosis in extremely obese 11-19 year olds was 16.14, when compared to
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children of the same age within the normal weight range.\(^6\) Given that the age was significantly higher in our cohort of children with PTCS during the pandemic, we suspect that pubertal or post-pubertal children accounted for the majority of the increased encounters in this group. We attempted to confirm this by comparing the proportion of children who were pre-pubertal before and during the pandemic, and we did not find a significant difference. However, our definition of puberty – greater than 11 years of age – though consistent with the definition used in previous studies of pediatric PTCS, is likely to underestimate the number of pubertal cases, especially in girls, the gender representing 96% of our pandemic related cases.\(^6,8,18,19\)

The increase in obesity in our cohort after COVID-19 restrictions parallels trends in childhood obesity during the pandemic.\(^10\) In a population based study conducted at Children’s Hospital of Philadelphia, obesity prevalence increased from 13.7% (June to December 2019) to 15.4% (June to December 2020) during the pandemic. This increase was seen in all age groups. However, minorities and lower socio-economic groups were disproportionately affected. Racial and ethnic differences in rates of obesity increased from 10-11% to 13-14% during the pandemic. These findings are consistent with our report that racial and ethnic minorities were primarily affected by the increase in pediatric PTCS during the pandemic. Although much work is needed to understand the cause of this disparity, possible explanations include decreased access to outdoor spaces for physical activity and disproportionate reliance on schools to provide nutritious meals in minorities and lower income families.\(^10\)

Although we consider increased obesity to be the most likely explanation for the increase in PTCS during the pandemic, we cannot rule out direct effects of the SARS-CoV-2 virus on the
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central nervous system. None of our patients had a positive SARS-CoV-2 test at the time of admission. However, most patients were not tested for SARS-CoV-2 antibodies. Thus, we do not know whether prior infection could have affected CSF production or outflow. None of our patients had multisystem inflammatory syndrome in children (MIS-C), which has been previously reported in a child with PTCS during the pandemic.\(^{20}\)

More severe disease was found in children during the pandemic, as manifested by worse visual acuity and a greater proportion of children with fulminant presentation and requiring surgical treatment. This may be related to the higher rates of obesity during the pandemic. Szewka and colleagues found that obese patients with PTCS were more likely to have severe papilledema and severe vision loss.\(^{21}\) We suspect that visual field defects were likely worse during the pandemic, since peripheral field defects are generally believed to precede central vision loss in children, as in adults with PTCS.\(^{22}\) However, we did not find a significant difference when comparing visual field defects before and during the pandemic. Our analysis was significantly hampered by the inconsistencies in the types of visual field testing performed, such that we could not perform analyses on visual field indices such as mean deviation and could only reliably compare whether patients had a field defect other than an enlarged blind spot. Similarly, we could not reliably compare grade of papilledema or RNFL thickness, due to incomplete reporting of Frisen grade in the medical record, inconsistent ordering of ancillary tests (fundus photographs and OCTs), and inaccuracies of the automated OCT algorithm in segmenting the RNFL in eyes with severe papilledema.
Another possible contributing factor to the increased rate of emergency department visits and inpatient admissions for PTCS during the pandemic may be delay of care related to families being unwilling or unable to come to the hospital for outpatient visits. We did not assess the duration of symptoms in all patients, but those with fulminant PTCS (23% of the pandemic cohort) had headaches for less than two weeks and vision loss for less than one week prior to presentation. Additionally, although other clinics may have restricted access to outpatient clinics for new patients during the pandemic, this was not the case at our hospital.

The limitations of our study include its retrospective nature with inconsistent and incomplete data on visual fields, papilledema grade, and OCT RNFL thickness. Additionally, due to the absence of Tanner staging, we used age as a surrogate for puberty, which may have led to inaccuracies in our calculation of the proportion of pre-pubertal patients in each group. The age of pubertal onset has been decreasing worldwide, particularly in girls. The average age at which girls manifested the first sign of puberty, thelarche, decreased from 10.5 to approximately 9.7 years between 1977 and 2013. Thus, the traditional cutoff of 11 years to divide pre-pubertal and pubertal children is likely outdated, but was used in this study because of the lack of any available data to make a more accurate pubertal determination. Race and ethnicity data were also incomplete, with 15-17% of patients categorized as “other” or “unknown.” Finally, our study was conducted at a tertiary care children’s hospital serving an urban population, and the results may not generalize to other settings.

In conclusion, we report a significant increase in emergency department visits, inpatient admissions, and surgical interventions for pediatric PTCS during the COVID-19 pandemic. This
Pediatric pseudotumor cerebri admissions during COVID-19 pandemic increase may be related to increased rates of childhood obesity during the pandemic, which is likely multifactorial but appears to disproportionately affect minority racial and ethnic groups. Further research is necessary to identify interventions to reduce the impact of the pandemic on childhood obesity, which may in turn reverse the upward trend in PTCS, a chronic condition with significant visual morbidity. As the pandemic begins to wane and restrictions are eased, the focus must be on weight loss and preventing further weight gain through dietary and physical fitness interventions. Physicians, parents, schools, and communities are encouraged to advocate for policies aimed at combating childhood obesity.24
References

Table 1. Comparison of inpatient admissions and emergency department visits for pediatric pseudotumor cerebri syndrome (PTCS) before and after March 19, 2020 (date of California stay at home order for COVID-19 pandemic). Unless otherwise specified, medians (ranges) are reported. *p<0.05

<table>
<thead>
<tr>
<th></th>
<th>Before pandemic: 3/20/2015 to 3/19/2020 (n=36 admissions)</th>
<th>During pandemic: 3/20/2020 to 2/20/2021 (n=26 admissions)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>14 (4 to 18)</td>
<td>16 (9 to 17)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Pre-pubertal (%)a</td>
<td>11 (31%)</td>
<td>3 (12%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6 (17%) / 30 (83%)</td>
<td>1 (4%) / 25 (96%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Race and ethnicity (%)</td>
<td></td>
<td></td>
<td>0.02*</td>
</tr>
<tr>
<td>Black</td>
<td>4 (11%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>14 (39%)</td>
<td>20 (77%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>11 (31%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Other or unknown</td>
<td>6 (17%)</td>
<td>4 (15%)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (BMI) Z-score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (5 to 85)</td>
<td>32 (14 to 49)</td>
<td>39 (25 to 51)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Overweight (85 to 95)</td>
<td>2.0 (-1.2 to 4.8)</td>
<td>2.7 (1.5 to 3.6)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Obese (&gt;95)</td>
<td>7 (20%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Secondary PTCS (%)</td>
<td>9 (25%)</td>
<td>4 (15%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Emergency department / inpatient admission (%)</td>
<td>8 (22%) / 28 (78%)</td>
<td>6 (23%) / 20 (77%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Opening pressure (cm H₂O)</td>
<td>42 (27 to 63)</td>
<td>48 (30 to 55)</td>
<td>0.22</td>
</tr>
<tr>
<td>Fulminant presentation (%)</td>
<td>2 (6%)</td>
<td>6 (23%)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Visual acuity (logMAR), averaged between 2 eyes</td>
<td>0.05 (-0.12 to 0.59)</td>
<td>0.14 (0 to 0.92)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Visual field defect other than enlarged blind spot (%)</td>
<td>11 (31%)</td>
<td>14 (54%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Abducens palsy (%)</td>
<td>9 (25%)</td>
<td>5 (19%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Surgical intervention (%)</td>
<td>2 (6%)</td>
<td>6 (23%)</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

aYounger than 11 years of age was considered pre-pubertal.
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Table 2. Characteristics of children presenting with fulminant pseudotumor cerebri syndrome (PTCS) between March 20, 2015 and February 20, 2021. Unless otherwise specified, medians (ranges) are reported.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fulminant PTCS (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>16 (13 to 17)</td>
</tr>
<tr>
<td>Pre-pubertal (%) ^a</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>0 (0%) / 8 (100%)</td>
</tr>
<tr>
<td>Race and ethnicity (%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Body mass index (range) Z-score</td>
<td>40 (25 to 49)</td>
</tr>
<tr>
<td>BMI category (percentile)</td>
<td>2.6 (1.5 to 3.8)</td>
</tr>
<tr>
<td>Normal (5 to 85)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Overweight (85 to 95)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Obese (&gt;95)</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Secondary PTCS (%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Opening pressure (cm H₂O)</td>
<td>54 (39.5 to 60)</td>
</tr>
</tbody>
</table>
Figure Legends

Figure 1. Number of emergency department visits and inpatient admissions for pediatric pseudotumor cerebri syndrome per month at our institution between March 19, 2015 and February 20, 2021. The arrow marks the start of the statewide stay-at-home order on March 19, 2020.
Supplemental Table 1. Types of visual field (VF) defects (other than an enlarged blind spot) in children with abnormal visual fields evaluated by Humphrey, Goldmann, and confrontational VF testing before and during the COVID-19 pandemic.

<table>
<thead>
<tr>
<th></th>
<th>Before pandemic: 3/20/2015 to 3/19/2020 (n=11 abnormal VF)</th>
<th>During pandemic: 3/20/2020 to 2/20/2021 (n=14 abnormal VF)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Humphrey VF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal defect</td>
<td>2 (18%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Arcuate defect</td>
<td>5 (45%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Quadrantanopia</td>
<td>0</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Generalized depression</td>
<td>0</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Peripheral constriction</td>
<td>0</td>
<td>2 (14%)</td>
</tr>
<tr>
<td><strong>Goldmann VF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal defect</td>
<td>3 (27%)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral constriction</td>
<td>1 (9%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td><strong>Confrontational VF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral constriction</td>
<td>0</td>
<td>1 (7%)</td>
</tr>
</tbody>
</table>
Statement of Authorship

1. Category 1:
   a) Conception and design
      Melinda Chang, Mark Borchert
   b) Acquisition of data
      Melinda Chang, Mark Borchert
   c) Analysis and interpretation of data
      Melinda Chang, Cindi Yim, Mark Borchert

2. Category 2:
   a) Drafting the manuscript
      Melinda Chang, Cindi Yim, Mark Borchert
   b) Revising it for intellectual content
      Melinda Chang, Cindi Yim, Mark Borchert

3. Category 3:
   a) Final approval of the completed manuscript
      Melinda Chang, Cindi Yim, Mark Borchert