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Short communication

High prevalence of pineal cysts in adults who stutter

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1. Introduction

Pineal cysts are a common incidental finding noted on brain magnetic resonance imaging (MRI). Cysts over 5 mm in diameter occur from 1% to 4% (Al-Holou, Garton, Muraszko, Ibrahim, & Maher, 2009; Al-Holou et al., 2011; Gur et al., 2013; Nevins et al., 2016; Sawamura et al., 1995; Sener, 1995; Sullivan et al., 2016), with a much larger occurrence of smaller cysts (Nolte, Brockmann, Gerigk, Groden, & Scharf, 2010; Pu et al., 2007; Whitehead, Oh, & Choudhri, 2013). Pineal cysts are typically benign, asymptomatic and remain stable in size across time (Nevins et al., 2016). In rare cases cysts may enlarge causing headaches, ocular movement abnormalities, secondary parkinsonism, ataxia and obstructive hydrocephalus (Gore, Gonzalez, Rekate, & Nakaji, 2008; Morgan et al., 2008).

The pineal gland is a midline neuroendocrine brain structure located immediately above the midbrain and between lobes of the thalamus. It is involved in sleep regulation through secretion of melatonin and may also play a role in pubertal development (Silman, Leone, Hooper, & Preece, 1979). Pineal cysts are circumscribed, fluid-filled lesions with a three layered wall; an outer fibrocollagenous rim, an intermediate pineocyte layer and an inner glial layer (Whitehead et al., 2013). The pineal gland forms early in embryologic development out of a diverticulum of the developing third ventricle. The etiology of pineal cysts is unknown, but several hypotheses exist. In some cases, remnants of the diverticulum form a cavity lined by ependymal cells which may proliferate to form a cyst (Osborn & Preece, 2006). Alternative hypotheses propose, pineal cysts may develop secondary to focal degeneration of the pineal gland (Kahilogullari, Massimi, & Rocco, 2013) due to hemorrhage or necrosis of the pineal gland during fetal development (Laure-Kamionowska, Maślińska, Deregowski, Czichos, & Raczkowska, 2003), or cysts may develop from necrosis or cavitation of pineal gland following the ischemic degeneration (Bregant, Rados, Derganc, Neubauer, & Kostovic, 2011).

An increased prevalence of pineal cysts have been associated with some disorders. For example, Gupta et al. (2016) found that 50% of children with familial retinoblastoma had pineal cysts. They hypothesized that cyst development may be a consequence of altered biology induced by the specific gene mutations related to familial retinoblastoma. An investigation of children with cerebral palsy and periventricular leukomalacia demonstrated a 32.3% prevalence of pineal cysts (Ozmen et al., 2015). Besides increased prevalence in some disorders, Gur et al. (2013) found that Caucasians were 195% more likely than African Americans to have a pineal cyst. There is also evidence that pineal cysts are more prevalent in females compared to males (Al-Holou et al., 2009; Sawamura et al., 1995; Sullivan et al., 2016). These examples demonstrate that genetic or hormonal factors may play a role in the pathobiological mechanisms of pineal cysts development.

Developmental stuttering is a neurodevelopmental disorder that typically first presents between two and four years of age (Chang, 2014). It is estimated that 75%, or more, of children who begin stuttering will outgrow it within a few years of onset (Yairi & Ambrose, 2013). Consistent with other neurodevelopmental disorders, there is a higher prevalence of stuttering in males compared to females (Bloodstein & Ratner, 2008). Subtle structural and functional differences have been discovered in the brains of adults who stutter (AWS), and more recently in children who stutter, compared to fluent speakers (for reviews see Chang, 2014; Etchell, Civier, Ballard, & Sowman, in press). The most robust findings are related to aberrant white matter tracts in the left hemisphere connecting critical speech motor areas (e.g. superior longitudinal fasciculus, arcuate fasciculus). Chang, Zhu, Choo, and Angstadt (2015) found that these white matter tract deficits exist in children close to the age of stuttering onset and may be part of the neurobiological basis of the disorder. There is evidence that white matter deficits may result from abnormal post-natal myelogenesis (Cykowski, Fox, Ingham, Ingham, & Robin, 2010). The frequently observed increased right hemisphere functional activity during speech tasks in AWS is likely related to compensation for left hemisphere structural deficits (Sowman, Crain, Harrison, & Johnson, 2014). The familial heritability of stuttering and recent linkage and association studies provide support that there is a genetic component involved in the neurodevelopment of stuttering (Frigerio-Domingues & Drayna, 2017). However stuttering is not a simple genetic disorder, and understanding comorbid features (e.g. pineal cysts) may provide information on shared neurodevelopmental processes.

While conducting a study of the neural correlates of stuttering

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(primary study) we encountered an unexpected high rate of pineal cysts on brain MRI scans of nine AWS. Because an association of pineal cysts and stuttering has not been reported previously, we decided to confirm this observation by comparing our cohort of AWS to 7858 research participants without known stuttering scanned at the same imaging center. Our hypothesis was that the incidence of pineal cysts would be greater in AWS than in our comparison cohort.

2. Results

2.1. Pineal cysts in the AWS

Of the nine AWS in this study, five (four males, one female) had a pineal cyst identified on the radiologic review, a prevalence of 55.6%. All of the radiologic reviews in the AWS study were conducted by the same neuroradiologist (#3). Typically the radiologists only indicate the existence of pineal cysts and a rough estimate of size (e.g., pineal cyst under 1 cm) in the radiologic reviews, so a certified MRI technologist and the first author reanalyzed the scans of the 5 AWS to obtain precise measurements of the cysts. After the measurements were completed, radiologist #3 confirmed the accuracy of measurement methods. Anteroposterior and craniocaudal measurements were taken from the sagittal plane, and included the cyst walls and in the case of septated cysts (e.g. participants 4 and 5) all divisions were measured as a single unit. Fig. 1 shows an enlarged image of the measurements for participant 5. Table 1 provides the pineal cyst measurements for each AWS participant. The average maximal cyst dimensions was 10.34 mm with a range of 8.9–12.6. Fig. 1 shows an example of the measurement methods on participant #1 and Fig. 2 shows images of the individual pineal cysts for participants #2–5.

2.2. Pineal cysts in the comparison sample

In total there were 413 individuals with pineal cysts and 7445 without pineal cysts, a prevalence of 5.26%. There were 212 males (4.37% prevalence) and 201 females (6.70% prevalence) with pineal cysts and the average age at scan was 29.0 years (range: 1–76). There was a significant difference in pineal cyst prevalence between males and females, X^2 (1) = 20.22, p < .001, OR = 1.57, 95% CI (1.29, 1.92).

Since all of the AWS scans were reviewed by radiologist #3, it was important to investigate differences in pineal cyst prevalence between radiologists to test for radiologist bias. Radiologist #2 had a significantly greater prevalence (6.87%) than radiologist #1 (3.95%), X^2 (1) = 25.44, p < .001, OR = 1.80, 95% CI (1.43, 2.26), radiologist #3 (9.91%) had a significantly greater prevalence than radiologist #1, X^2 (1) = 60.21, p < .001, OR = 2.68, 95% CI (2.07, 3.46), and radiologist #2, X^2 (1) = 7.34, p = .007, OR = 1.49, 95% CI (1.12, 2.00).

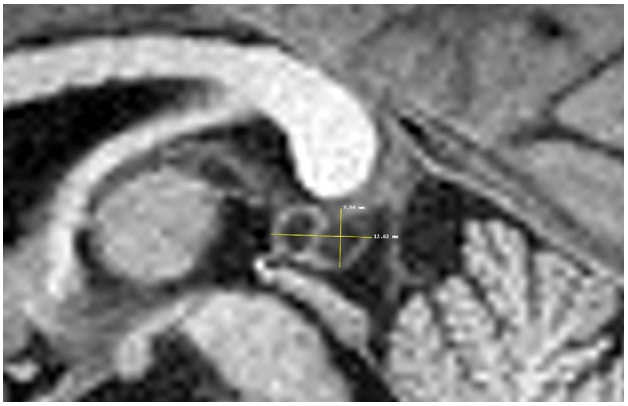

Fig. 1. Enlarged sagital T-1 weighted MR image of participant #1 pineal cyst. The lines show the anteroposterior (12.62 mm) and craniocaudal (7.34 mm) measurements. All measurements included the cyst walls.

It has been argued that scanners with greater resolution make the detection of pineal cysts more likely (Nolte et al., 2010). In our sample, on a 1.5 T scanner there were 3029 scans without pineal cysts and 39 with cysts, a prevalence of 3.9%. On the 3 T scanners there were 4932 scans without pineal cysts and 310 with cysts, a prevalence of 5.9%. To explore a scanner resolution effect we compared the prevalence of pineal cyst detection across the total number of scans for each scanner type. The 3 Tesla scans had a significantly greater prevalence than the 1.5 Tesla scans, X^2 (1) = 16.28, p < .001, OR = 1.55, 95% CI (1.25, 1.92).

2.3. Comparison of AWS to overall sample prevalence

Using a 2-sample test for equality of proportions with continuity correction we compared the prevalence in the AWS (55.6%) to the overall prevalence of pineal cysts in the large sample from the radiologic review database (5.3%). Despite the small sample size of AWS, there was a significant difference in the prevalence between the two groups, X^2 (1) = 35.76, p < .001, OR = 22.53, 95% CI (6.03, 84.23). Stated another way, there is 95% confidence that the odds of an AWS having a pineal cyst is 6–84 times greater than a person without known stuttering.

Given that radiologist #3 had a significantly higher pineal cyst prevalence and this was the only reviewer for the AWS group, a secondary analysis was conducted to ensure a valid comparison. We compared the prevalence of pineal cysts in the AWS to the smaller subset of the radiologic reviews that were conducted by radiologist #3 (87 with and 791 without pineal cysts; 9.9%). Again, there was a significant difference in the prevalence between the AWS and the comparison group, X^2 (1) = 15.39, p < .001, OR = 11.37, 95% CI (3.00, 43.11). Based on this subset analysis there is 95% confidence that the odds of an AWS having a pineal cyst is 3–43 times greater than a person without known stuttering.

3. Discussion

The prevalence of pineal cysts was significantly higher in the AWS compared to a large sample of people with no known stuttering. The comparison was valid for two reasons. First, the comparison group was imaged at the same facility and radiologic reviews followed similar procedures for reporting. An additional analysis to ensure that the difference was not due to radiologist bias was also significant. Secondly, the results from our comparison sample are consistent with the current research. For example, the overall prevalence of pineal cysts at this site (5.3%) is consistent with other studies with large sample sizes that used similar criteria for pineal cyst identification (e.g. ≥ 5 mm) (Al-Holou et al., 2009, 2011; Gur et al., 2013; Nevins et al., 2016; Sawamura et al., 1995; Sener, 1995; Sullivan et al., 2016). The two largest studies that used a criteria of cysts greater than 5 mm had samples of 48,417 (Al-Holou et al., 2011) and 42,099 (Nevins et al., 2016) MRI scans and found prevalences of 1% and 0.67% respectively. It's important to note that all of the AWS had cysts well above 5 mm (M = 10.5, range: 8.9–12.6). Consistent with other studies, our comparison sample also showed a greater prevalence of pineal cysts in females compared to males (Al-Holou et al., 2009; Sawamura et al., 1995; Sullivan et al., 2016), and greater detection of cysts on scanners with greater resolution (Nolte et al., 2010; Pu et al., 2007).

Stuttering is a neurodevelopmental disorder (Chang, 2014) with consistent characteristics of onset, recovery patterns, sex differences, and family heritability (Bloodstein & Ratner, 2008). No single factors has been identified that is necessary or sufficient to cause stuttering (Smith & Kelly, 1997), however, neuroimaging and genetics research point to a primary causal role of neural developmental deficits within the speech production system (Frigerio-Domingues & Drayna, 2017;

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