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Is the Pineal Cyst a Relevant Issue for Autism?

The co-occurrence of pineal cyst and autism spectrum disorders

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Abstract

Objectives: Evaluate the simultaneous occurrence between pineal cysts and children diagnosed with autism spectrum disorders in order to understand a possible relevance of pineal gland in ASD.

Experimental procedures: Retrospective case-control study carried out on 161 children: 93 cases diagnosed with autism spectrum disorder (38 with level 1 severity and 55 with level 2 severity) were compared with 68 controls (non-autistic patients). All participants had done a magnetic resonance image and were patients of the child psychiatry department.

Results: This study shows that the prevalence of pineal cysts is higher in autistic children comparing with non-autistic children (84.6% *vs.* 15.4%, p=0.041). If the level of severity of the autism is discriminated into level 1 and 2, there is also a significant difference between these groups (15.4% *vs.* 84.6% *vs.* 0.0% in non-autistic, level 1 and level 2 ASD, respectively, p<0.001). The latter association was analysed calculating the odds of the presence of pineal cyst and having level 1 autism which was increased but with a wide variability (OR, 95% CI 13.75, [2.38-79.38]).

Conclusion: This study shows a correlation between pineal cysts and autism spectrum disorders. There are differences when comparing the presence of pineal cysts between children with ASD and non-autistic children (p=0.041). This association is stronger in the children diagnosed with level 1 or mild ASD (p=0.001), since it is the group with the highest prevalence of pineal cysts (11.8%) much higher than the general population (ranges from 0.8% to 2.5%). The odds ratio calculated in this study reveals that patients with pineal cysts have 3 times higher association with mild ASD. All these findings help to corroborate the higher prevalence of pineal cysts in the autistic population when compared to the general population and suggest some relevance of pineal gland in autism.

Keywords: Autism spectrum disorders; Pineal cyst; Magnetic resonance imaging findings

Highlights

- This study shows a high prevalence of pineal cysts in autistic children compared with non-autistic patients.
- Level 1 autism has the highest number of cases with pineal cysts comparing to level 2 autistic and non-autistic patients.

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder, with persistent impairment in reciprocal social communication, social interaction, and restricted, repetitive patterns of behaviour, interests or activities. ASD is classified by severity of the disease, according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), in level 1, 2 and 3 (mild, moderate and severe, respectively). The prevalence approaches 1% of the population worldwide [1-3].

Imaging tests are useful for investigation of visual and hearing impairment, co-morbid conditions, epilepsy or focal neurological deficits [4]. Several studies with Magnetic Resonance Imaging (MRI) have shown incidental findings typically gross abnormalities, focal lesions, or structural variations of normal [5]. There are different findings and their high prevalence may be an important tool in clinical assessment as suggested by some authors [5-7]. Pineal cysts, arachnoid cysts, choroid plexus cysts, enlarged perivascular spaces, cavum septum pellucidum, asymmetrical ventricles are some of the MRI incidental findings described in

children diagnosed with ASD, paediatric population and the general population [5,6,8-10].

Previous studies have reported a prevalence of pineal cysts, on studies considering general population, raging 1 to 2,5%, being more close to 1% in larger studies [8-15]. These are found more frequently in young adults, in girls and are rare in children younger than 10 years of age [11]. The majority of the studies acknowledge the cyst identification when it has more than 5 mm in a single plane, well circumscribed, homogenous [10,13,14]. Associations with other diseases haven't been found, and they are most commonly considered an asymptomatic and benign finding that most likely will suffer involution in adulthood [9,10,13,14].

Literature propose that one of the biological causes of autism is malfunction of the pineal gland and deficiency of its principal hormone, melatonin. The main function of melatonin is to link and synchronize the body's homeostasis processes. Pineal dysfunction has been implicated based on the common observation of low melatonin levels and sleep disorders associated with autism. Abnormal neuroplasticity may be explained by hyperactivity of endogenous N, N-dimethyltryptamine (DMT) produced in pineal gland, according to some authors [16].

So it would be interesting to evaluate the co-occurrence between the presence of pineal cyst and ASD because it would reinforce the importance of the function of pineal gland in autism.

Experimental Procedures

Study design, database and sampling

This is a retrospective case-control study designed with child psychiatry appointment patients of the Centro Hospitalar São João, Porto, Portugal. Data was collected using the clinical issues recorded in the "SClinico Hospitalar" platform. This program is used by National Health System of Portugal, and contains all information of the patients' health and their additional diagnostic exams. Information does not uncover the patient's identity at any moment.

The database created includes the following variables: date of birth, gender, date of the patient's first MRI, presence of pineal cyst, presence of other MRI finding (includes all different findings except pineal cysts) and presence of ASD or other.

All ASD patients in the current study were diagnosed accordingly by the DSM-V, including two main psychopathological domains: social communication and restricted, repetitive behaviours. The severity was discriminated as level of support needed for each domain as: level 1 (requiring support), level 2 (requiring substantial support) and level 3 (requiring very substantial support) [1]. To help the clinical diagnostic it was used Child Autism Rating Scale (CARS) and the standardized Autism Diagnostic Interview-Revised (ADI-R) which provides a diagnostic algorithm for autism and consists on an interview designed to assess the developmental history of autistic behaviours [17].

The cases and controls were patients that attended the appointments from September 2016 to the end of January 2017. Inclusion criteria were: patients diagnosed with ASD and a control group with patients without ASD which all had a MRI report. Exclusion criteria were: all patients without a MRI or without its report in the platforms.

Statistical analysis

Considering the inclusion and exclusion criteria previously listed, in this study were analysed 161 children. Descriptive and univariate analysis were performed using independent T test for continuous variables and Chi-square for categorical ones. Because actual age and age at the moment of the MRI are variables with a non-normally distribution, we used the non-parametric Mann-Whitney test.

We also used logistic regression in order to evaluate the odds ratio of pineal cysts in level 1 and 2 ASD, adjusting for child's sex, and posteriorly, for child's sex and age.

The significance level was set at $p<0.05$. The statistical analysis was made using Statistical Package for Social Sciences (SPSS) for macOS Sierra, version 24.0.

Results

This study has 161 children enrolled, 93 cases (patients diagnosed with ASD) and 68 controls (patients without an ASD diagnostic). The median age (Percentile 25th-Percentile 75th) was 12.0 (8.0-14.0) years. Table 1 shows the actual age, the age at the moment of the MRI, and the different MRI findings between cases and controls. Significant differences were found relatively to the actual age and the age at the moment of the MRI between cases and controls, revealing that ASD diagnosed patients do MRI exams earlier, at the age of 5.0 (2.0-8.0) years than non ASD patients. No differences were found between the

Table 1: Age of children, age at the moment of the MRI and frequency of observed MRI findings, by presence or absence of ASD.

	ASD	Without ASD	
	n=93 (57, 8%)	n=68 (42, 2%)	p
Age (in years)[a]			
Actual	11.0 (7.0-13.0)	13.0 (9.0-15.0)	0.007
At the moment of MRI	5.0 (2.0-8.0)	8.0 (2.0-12.0)	0.007
MRI Findings[b]			0.186
Pineal cyst	11 (11.8%)	2 (2.9%)	
Septum pellucidum cyst	2 (2.2%)	5 (7.4%)	
Choroidal fissure cyst	4 (4.3%)	1 (1.5%)	
Cavum velum interpositum cyst	2 (2.2%)	0 (0.0%)	
Subependymal cyst	1 (1.1%)	0 (0.0%)	
Incomplete rotation of a hippocampus	0 (0.0%)	2 (2.2%)	
Adenohypophysis asymmetry	0 (0.0%)	1 (1.1%)	
Arachnoid granulation	0 (0.0%)	1 (1.1%)	
Transverse sinus asymmetry	0 (0.0%)	1 (1.1%)	
Lateral ventricle asymmetry	1 (1.1%)	1 (1.1%)	
Enlarged perivascular spaces	0 (0.0%)	1 (1.1%)	
Frontal basal venus's anomaly	0 (0.0%)	1 (1.1%)	
No findings	59 (86.8%)	65 (69.9%)	
Other MRI findings (excluding pineal cysts)			0.142
Without any finding	61 (89.7%)	76 /81.7%)	
With other cysts	6 (8.8%)	9 (9.7%)	
With the remaining findings	1 (1.5%)	8 (8.6%)	

[a]The values presented are median (95% CI).
[b]The values presented are n (%).

cases' and controls' MRI findings; nevertheless the prevalence of pineal cysts in ASD diagnosed patients is 11, 8% and 2.9% in the non-autistic patients. When analysing all the MRI findings, except for the pineal cysts, there were no statistical significant differences.

Table 2 discriminates age, MRI findings and ASD diagnosis by gender. It shows that age at the moment of MRI and the diagnosis of ASD (even if discriminated by level of severity) are significantly different. We found that male children do a MRI earlier in life than female patients (median of 4.5 years *vs.* 7.0 years, p=0.009) as well as there are more male patients diagnosed with ASD (66.4% *vs.* 39.2%, p=0.001). It is important to highlight the prevalence of 7.3% (n=8) in male patients and 9.8% (n=5) in female patients that had pineal cysts on their MRI reports. From those 5 girls, only 2 of them were from the control group.

When analysed accordingly to values of pineal cyst [Table 3], there were statistic differences when comparing the presence of this kind of cysts with ASD or non ASD diagnosed patients (84.6% *vs.* 15.4%, p=0.041). If the ASD diagnostic is discriminated by severity there is also a significant difference (15.4% *vs.* 84.6% *vs.* 0.0% in non-ASD, level 1 ASD and level 2 ASD, respectively, p<0.001), this is due to the presence of 11 cases (84.6% of all pineal cysts in the study) with the level 1 ASD severity.

In multivariable logistic regression [Table 4] between the presence of pineal cyst and ASD, adjusted to gender, we found that the presence of pineal cyst was associated with the odds of having a ASD diagnosis (OR [95% CI], 5.421 [1.104-26.616]) and this odds is greatly increased when a child has a level 1 ASD diagnosis, but with a wide variability (16.593 [3.194-86.203]). When adjusted to gender, but also adjusted to the age at the moment of MRI, this association maintains the significant difference, the presence of pineal cyst was associated with an odds ratio of having level 1 ASD (OR=20.575) and an odds ratio of having ASD (level 1 or level 2) (OR=8.516), but both associations with a wide variability (95% CI [3.599-117.622], and [1.481-48.972], respectively).

Table 2: Age of children and age at the time of the MRI, pineal cysts, other MRI findings and ASD by gender.

	Male	Female	
	n=110 (68.3%)	n=51 (31.7%)	p
Age (in years)			
Actual	12.0 (8.0-14.0)	12.0 (9.0-15.0)	0.359
At the moment of MRI	4.5 (2.0-9.0)	7.0 (3.0-11.0)	0.005
Pineal cyst			0.583
With cyst	8 (7.3%)	5 (9.8%)	
Without cyst	102 (92.7%)	46 (90.2%)	
Other MRI findings			0.369
Without any finding	95 (86.4%)	42 (82.4%)	
With other cysts	8 (7.3%)	7 (13.7%)	
With the remaining findings	7 (6.4%)	2 (3.9%)	
With or without ASD (discriminated by severity)			0.005
Level 1 (mild)	29 (26.4%)	9 (17.6%)	
Level 2 (moderate)	44 (40.0%)	11 (21.6%)	
Without ASD	37 (33.6%)	31 (60.8%)	
With or without ASD			0.001
ASD	73 (66.4%)	20 (39.2%)	
Without ASD	37 (66.4%)	31 (60.8%)	

The values presented are median (95% CI) or n (%).

Table 3: Age of children and at the time of the MRI, gender, ASD by pineal cyst.

	Without pineal cyst	With pineal cyst	
	n=148 (91.9%)	n=13 (8.1%)	p
Age (in years)			
Actual	12.0 (8.0-14.0)	12.0 (7.0-14.0)	0.661
At the moment of MRI	5.0 (2.0-10.0)	8.0 (3.0-s12.0)	0.255
With or without ASD (discriminated by severity)			<0.001
Level 1 (mild)	27 (18.2%)	11 (84.6%)	
Level 2 (moderate)	55 (37.2%)	0 (0.0%)	
Without ASD	66 (44.6%)	2 (15.4%)	
With or without ASD			0.041
ASD	82 (55.4%)	11 (84.6%)	
Without ASD	66 (44.6%)	2 (15.4%)	

The values presented are median (95% CI) or n (%).

Table 4: The effect of having pineal cysts on ASD discriminated by severity and grouped ASD comparing with non ASD.

ASD	Adjusted OR (95% CI)	p
Level 1 ASD	16.593 (3.194-86.203)[c]	0.001
Level 2 ASD	0.000 (0.000-0.000)[c]	0.997
Level 1 and 2 ASD	5.421 (1.104-26.616)[c]	0.037
Level 1 ASD	20.575 (3.599-117.622)[d]	0.001
Level 2 ASD	0.000 (0.000-0.000)[d]	0.997
Level 1 and 2 ASD	8.516 (1.481-48.972)[d]	0.016

[c]Logistic mode adjusted for child's gender.
[d]Logistic mode adjusted for child's gender and age at the moment of MRI.

Discussion

The objective of this study was to evaluate if there is any association between the presence of pineal cysts in MRI and children diagnosed with ASD in order to find some correlation between pineal gland and ASD as suggested by some authors [16]. Through the analyses of the results, there are differences when comparing the presence of pineal cysts between children with ASD and the control group (statistically significant, with p=0.041). This difference is even more striking if the level of the disease is taken into account (p=0.001), because all the cases with pineal cysts belongs to patients with level 1 or mild ASD. There are studies comparing the presence of incidental findings in ASD with control groups but showing no statistically significant association between these events [5,18,19]. This can be due to different study designs or a larger number of patients in this current study, as well as the fact that this study discriminates and analyses the pineal cyst alone with ASD patients providing a more efficient comparison.

Several studies on children and teenagers describe associations between incidental findings in ASD but no significant correlations

between brain imaging findings and autism were established [5,8,9,17]. Even comparing by gender, by presence or absence of ASD diagnosis or grouping cysts from the other findings, there are no statistically significant differences. But looking in more detail to the pineal cysts a correlation can be established.

The prevalence of pineal cysts found in different studies using general population ranges between 1 and 2, 5%, this numbers are more consistent if the population is of young age [11]. This study shows a high prevalence of pineal cyst among children (8.1% among all patients of the study) and even higher within the ASD's population (11.8%). This value is much higher when comparing to the prevalence of pineal cyst on general population found in different studies [8,10,14,20]. In one latest clinical report, it refers that pineal cysts are unusual in infants, its' peak is in young adulthood and are found more frequently in girls than in boys in all age groups [13]. Through the analysis of the database we found a higher prevalence of pineal cysts in the female group (9.8% *vs.* 7.3% in the male group), but it is relevant that all male patients with pineal cysts are ASD diagnosed children, whereas in the control group the 2 patients with pineal cysts are female. The median age of children at the moment of MRI (the moment when it is revealed the presence of pineal cyst) is 5 years old for autistic patients, and what is referred in literature is that the presence of this finding is rare in children younger than 10 years old [11,14].

The most important association of this study is the fact that the difference of having a pineal cyst in autistic children comparing with non-autistic population is statistically significant (p=0.041), especially when ASD severity levels are discriminated (more prevalent on level 1 ASD, with p=0.001). The latter is due to the fact that most pineal cysts encountered in this study are from level 1 (mild) ASD patients (11 patients). Furthermore, patients having pineal cyst are associated with increased odds (OR=16.6) in children with level 1 ASD, adjusted to gender, when comparing with non-autistic children. The odds is even higher (OR=20.6) when adjusted to gender and to the age at the moment of the MRI. Although the odds have a wide 95% CI ([3.194-81.203] for the first association and [3.599 -117.622] for the second) representing a great variability, there is an odds of at least 3 when comparing this aspects, which represents the minimum value of the CI. The fact that a patient with pineal cyst has 3 times higher association with ASD may suggest an important correlation between the function of pineal gland and autism.

We can propose a hypothesis that malfunction of pineal gland may be related with deficiency of melatonin and we know that melatonin is linked to body's homeostasis, antioxidant properties and immunomodulation [21]. Some authors relate this malfunction with sleep disorders and some immune deregulation in autism [22]. Another hypothesis is that the dysfunction of pineal gland may be related with abnormal metabolism of N-dimethyltryptamine which could explain abnormal neuroplasticity and neuronal distribution that can be found in some cases of autism [16].

Conclusion

In conclusion, this study shows a relation between the presence of pineal cyst and ASD, the high odds when these two events are associated suggests some questions about the importance of this correlation.

We may ask if the presence of pineal cyst has some relation with ASD level, and if pineal gland dysfunction may have some kind of relevance in ASD? Could it be the missing link related with some neuronal transmission? Is there a possible correlation between the genetic mutation of ASD's patients and the presence of pineal cyst? These questions are new challenges for further studies.

This study had some limitations like only including patients from Child Psychiatry appointments, as patients of the same hospital centre. However, it may play as an advantage because all ASD patients were diagnosed by the same criteria. It would be interesting if we could know the prevalence of pineal cyst in Portuguese population or even to have a control group that represented the general population. Also it would be important to follow the pineal cyst evolution of these patients in the future. Therefore, we recommend further studies with a larger sample size to understand this correlation.

Ethics

This study was approved by the Ethics Committee of Centro Hospitalar de São João-Faculdade de Medicina da Universidade do Porto.

Conflicts of Interest

None of the authors have any financial or nonfinancial competing interests concerning the present study. All the authors contributed equally to this work.

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