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Clinical markers of hyperactivity in patients with autism spectrum disorder

Marcadores clínicos de hiperatividade em pacientes com transtorno do espectro do autismo

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Abstract

Introduction: A comorbid diagnosis of Attention Deficit Hyperactive Disorder (ADHD) and Autism Spectrum Disorder (ASD) is associated with neuropsychological and neurophysiological changes, unlike those found in individuals with ASD but without ADHD. The comorbidity of the two disorders appears to further compromise the prognosis of individuals with ASD. The objective of the present study was to identify clinical characteristics that differentiate patients with ASD and hyperactivity from patients with ASD without hyperactivity. **Methods:** This is a case-control study, nested within a cross-sectional study, to analyze the clinical characteristics of individuals with ASD with and without hyperactivity. **Results:** The study sample consisted of 30 cases and 22 controls. The risk of hyperactivity was found to increase 4.5-fold when digestive complaints were present, 3.8-fold when dysarthria was present, 4.9-fold when concentration problems were present and 3.9-fold when there was psychomotor agitation. **Conclusion:** These findings suggest that the presence of symptoms of hyperactivity in individuals with ASD is associated with differences in their clinical profile, specifically a greater prevalence of complains of digestive abnormalities, dysarthria, psychomotor agitation and concentration problems.

Keywords: Autism, hiperactivity, ADHD, prevalence, gastrointestinal abnormalities.

Resumo

Introdução: um diagnóstico comórbido de transtorno do déficit de atenção e hiperatividade (TDAH) e transtorno do espectro do autismo (TEA) está associado a alterações neuropsicológicas e neurofisiológicas, ao contrário das encontradas em pessoas com TEA, mas sem TDAH. A comorbidade dos dois distúrbios parece comprometer ainda mais o prognóstico das pessoas com TEA. O objetivo do presente estudo foi identificar as características clínicas que diferenciam pacientes com TEA e hiperatividade de pacientes com TEA sem hiperatividade. **Métodos:** trata-se de um estudo caso-controle, aninhado a um estudo transversal, para analisar as características clínicas de indivíduos com TEA com e sem hiperatividade. **Resultados:** A amostra do estudo foi composta por 30 casos e 22 controles. Encontrou-se que o risco de hiperatividade aumenta 4,5 vezes quando há problemas digestivos, 3,8 vezes quando há disartria, 4,9 vezes quando há problemas de concentração e 3,9 vezes quando há agitação psicomotora. **Conclusão:** Esses achados sugerem que a presença de sintomas de hiperatividade em indivíduos com TEA está associada a diferenças no perfil clínico, especificamente maior prevalência de queixas de alterações digestivas, disartria, agitação psicomotora e problemas de concentração.

Palavras-chave: Autismo, hiperatividade, TDAH, predominância, anormalidades gastrointestinais.

Resumen

Introducción: Un diagnóstico comórbido de trastorno por déficit de atención con hiperactividad (TDAH) y trastorno del espectro autista (TEA) se asocia con cambios neuropsicológicos y neurofisiológicos, a diferencia de los que se encuentran en personas con TEA pero sin TDAH. La comorbilidad de los dos trastornos parece comprometer aún más el pronóstico de las personas con TEA. El objetivo del presente estudio fue identificar las características clínicas que diferencian a los pacientes con TEA e hiperactividad de los pacientes con TEA sin hiperactividad. **Métodos:** se trata de un estudio de casos y controles, anidado dentro de un estudio transversal, para analizar las características clínicas de individuos con TEA con y sin hiperactividad. **Resultados:** La muestra del estudio estuvo constituida por 30 casos y 22 controles. Se encontró que el riesgo de hiperactividad aumenta 4,5 veces cuando hay problemas digestivos, 3,8 veces cuando hay disartria, 4,9 veces cuando hay problemas de concentración y 3,9 veces cuando hay agitación psicomotora. **Conclusión:** Estos hallazgos sugieren que la presencia de síntomas de hiperactividad

en individuos con TEA se asocia con diferencias en el perfil clínico, específicamente una mayor prevalencia de quejas de trastornos digestivos, disartria, agitación psicomotora y problemas de concentración.

Palabras clave: Autismo, hiperatividade, TDAH, predominância, anormalidades gastrointestinales.

Introduction

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are the most prevalent neurodevelopmental disorders (APA, 2014). ASD is characterized by a deficiency in communication and reciprocal social interaction associated with restrictive or repetitive patterns of behavior (APA, 2014). ADHD is characterized by symptoms of motor hyperactivity associated with impulsiveness and difficulty in concentrating. The prevalence of ADHD symptoms in patients with ASD is estimated at around 50% (Pondé, Novaes & Losapio, 2010; Di Martino et al. 2013). A comorbid diagnosis of ADHD and ASD is associated with neuropsychological (Colombi & Ghaziuddin 2017) and neurophysiological changes, unlike those found in individuals with ASD but without ADHD (Yerys et al. 2019). Neuroimaging studies have shown reduced activation in the right inferior frontal cortex of patients with comorbid ASD/ADHD compared to those with ASD and no associated ADHD. Furthermore, in children with ADHD without ASD, activity in that region of the brain is also reduced (Lukito et al. 2018).

Comorbid ASD and ADHD may result in greater impairment to social and academic functioning (Gargaro, et al. 2018; Sinzig, Walter, Doepfner, 2009) There is a negative effect on quality of life that is a consequence of a greater number of emotional and psychosocial problems as well as difficulties associated with interpersonal relationships (Thomas, Sciberras, Lycett, Papadopoulos & Rinehart, 2018). Patients with this comorbidity often use more medication compared to individuals with ASD alone (Pondé, Novaes & Losapio, 2010). Children with comorbid ASD/ADHD often have more severely impaired short-term verbal memory, poorer control of executive functions, marked autistic traits and difficulties with adaptive functioning (Yerys et al. 2009). A study in which memory and learning were evaluated in high-functioning autistic individuals found greater impairment in verbal delayed recall and in short-term verbal working memory in the group with comorbid ADHD (Andersen, Hovik, Skogli, Egeland

& Oie 2013). Young people with high-functioning autism and ADHD often fail to receive adequate treatment, which may result in impairment in various areas, including academic performance and in social and emotional skills (Joshi et al. 2017). Therefore, the comorbidity of the two disorders appears to further compromise the prognosis of individuals with ASD.

Objectives

The objective of the present study was to identify clinical characteristics that differentiate patients with ASD and hyperactivity from patients with ASD without hyperactivity.

Methods

This was a case-control study nested within a cross-sectional study conducted with patients attending LABIRINTO, an interdisciplinary laboratory for research in autism, between January 2013 and May 2016. Patient records of individuals with ASD follow a standard model of anamnesis created to enable research to be carried out and to optimize patient care. All the patients attending the clinic are submitted to the same protocol: a medical resident conducts anamnesis with the child's parents based on the structured model used in the clinic. The child is then evaluated by the medical resident, psychology intern and by preceptors from the institute (a psychologist and a psychiatrist). In a clinical session involving the whole team, the medical resident presents the anamnesis, and the psychiatric examination of the child is discussed. The team discussion results in a list of problems and an ASD diagnosis may or may not eventually be made in accordance with the DSM-5 diagnostic criteria (APA, 2014). The fact that the same preceptors conduct the children's evaluation and participate in the clinical discussions guarantees the reliability of the diagnoses.

A total of 52 children were seen in this clinic between January 2013 and May 2016. Cases were defined as: children whose parents had reported hyperactivity as part of the child's medical history and for whom a description of hyperactivity was included in the list of problems and/or who had a diagnosis of comorbid ADHD. Controls were defined as children whose parents had not referred to hyperactivity when reporting the child's medical history, and those for whom hyperactivity had not been included in the

list of problems, and those with no comorbid diagnosis of ADHD. Patients with genetic syndromes or metabolic diseases associated with ASD, children under two years of age, those whose parents had reported the symptom of hyperactivity as part of their medical history but for whom hyperactivity was not included in the list of problems or in the diagnosis made by the evaluators were excluded from the study.

Sociodemographic and clinical data and family history were obtained from the clinical records. The sociodemographic data consisted of the following variables: sex, age, skin color, identification of the individuals living with the child, monthly per capita family income, and father and mother's education level. The clinical characteristics consisted of the variables obtained at anamnesis and those acquired at clinical evaluation of the child. The variables obtained at anamnesis were: medical history as reported by the parents (epilepsy, hyperactivity, hetero-aggressiveness, auto-aggressiveness, difficulty in concentrating, gait deviations, dysarthria, depression, anxiety, psychomotor agitation, defiant behavior and fear); complaints mentioned during systematic questioning (head, respiratory system, cardiovascular system, digestive system, genitourinary system and sleep); developmental milestones (age at first words, age at first phrases, duration of breastfeeding, age when starting walking, age when bladder control was achieved and age when bowel control was achieved); and family history (depression, bipolar disorder, alcohol consumption, use of drugs, schizophrenia, suicide or attempted suicide, intellectual disability, epilepsy and ASD). The clinical characteristics obtained at examination of the child were: verbal communication (does not speak, speaks using single words, speaks in simple phrases or speaks fluently) and the severity of ASD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (mild, moderate or severe) and according to the Clinical Global Impression scale (rated from 0 to 7).

Data analysis was conducted using the SPSS statistical software program, version 22. Logistic regression models were constructed to identify the variables predictive of an increased risk of hyperactivity in patients with ASD. The stepwise model was used in which the variables that are statistically significant in predicting the dependent variable (hyperactivity) are included. The variables for which there were statistically significant differences between the groups according to the chi-square test were used to construct the logistic regression models.

This study is nested within a larger project: “Autism phenotypes and symptoms of anxiety and depression in the parents”, which was approved by the internal review board of the Bahia School of Medicine and Public Health under reference CAAE 17985613.1.00005544 in accordance with the regulations defined under Resolution 466/12 of the Brazilian National Health Council that regulates the guidelines governing research involving human beings. All participant parents/guardians gave their written consent.

Results

Out of a sample consisting of children/adolescents with ASD, 30 were classified as cases (ASD with hyperactivity) and 22 as controls (ASD without hyperactivity). The majority of the children in both groups were under six years of age, male, black or brown-skinned, and with both parents living in the family home. In addition, most had siblings. Family income was similar in both groups, with half the participants having a per capita monthly family income of less than half a minimum salary. The majority of the parents in both groups had completed at least high school education. The majority of the children in both groups had: breastfed for at least six months; spoken their first phrases after 36 months of age or did not yet speak in phrases; walked before completing 18 months; and had achieved bladder and bowel control only after 36 months or had not yet achieved control. The diagnostic evaluation of ASD and the Clinical Global Impression scale scores were predominantly indicative of moderate severity in both groups. The most common factors listed in family history were depression and alcohol abuse, with no statistically significant difference between the groups. There were differences, however, with respect to the following variables. A medical history of dysarthria was significantly more common in the case group (73.3% versus 45.5%) as was a report of digestive problems (46.7% versus 18.2%) ($p < 0.05$). Complaints of difficulty in concentrating (86.7% versus 61.9%) and psychomotor agitation (66.7% versus 36.4%) were also more common in the case group ($p < 0.05$). The sociodemographic and clinical data of the children in the two groups are summarized in table 1.

Table 1: Sociodemographic and clinical characteristics of the children with autism spectrum disorder (ASD) in the two study groups

	ASD	
	With hyperactivity (%)	Without hyperactivity (%)
Age 2 to 6 years	80	59
Male	77	68
Brown-skinned	50	62
Father living in the home	60	73
Mother living in the home	93	95
Siblings in the home	53	73
Income less than 100 dollars / month	50	52
Father completed high school	65	68
Mother completed high school	69	68
Breastfed for six months or more	62	68
First words prior to 18 months of age	50	71
First phrases prior to 36 months of age	28	32
First steps before 18 months	68	82
Bladder control before 30 months	30	38
Bowel control before 30 months	24	40
Verbal language present	35	50
DSM-5 mild to moderate	73	73
Psychomotor agitation	66	37
Anxiety	50	54
Dysarthria*	73	46
Gait deviations	47	23
Difficulty in concentrating	87	62
Auto-aggressiveness	60	64
Hetero aggressiveness	70	59
Epilepsy	7	14
Respiratory complaint	63	55
Digestive tract complaint*	47	18
Genitourinary complaint	20	14
Sleep complaint	60	50

*P<0.05

Two logistic regression models were constructed to identify the best predictors of an increased risk of hyperactivity in patients with ASD. In model 1, the predictive variables were: digestive complaints and dysarthria (Table 2). The presence of digestive complaints resulted in a 4.5-fold increased risk and dysarthria in a 3.8-fold increased risk of hyperactivity.

Table 2: Model 1 in the logistic regression analysis conducted to identify the factors associated with the group of individuals with ASD and hyperactivity.

Model	Parameter	Estimation (B)	Standard Error (SE)	Wald	Odds Ratio	95% Confidence Interval	
						Lower limit	Upper limit
1	Constant	-0.118	0.344	0.118	0.889	-0.791	0.556
	Digestive complaints	1.371	0.663	4.274	3.937	0.071	2.670
2	Constant	-0.970	0.558	0.783	0.378	-2.068	0.121
	Digestive complaints	1.522	0.707	4.636	4.584	0.137	2.908
	Dysarthria	1.347	0.643	4.390	3.846	0.087	2.607

ASD: autism spectrum disorder.

Model 2 showed that the presence of the variable difficulty in concentrating resulted in a 4.9-fold increased risk and psychomotor agitation in a 3.9-fold increased risk of hyperactivity (Table 3). When attempting to construct a single model containing the four variables, no adequate psychometric indexes were found for this prediction, probably because the sample size did not confer sufficient power to enable a model with adequate psychometric indexes for the four variables to be constructed.

Table 3: Model 2 in the logistic regression analysis conducted to identify the factors associated with the group of individuals with ASD and hyperactivity

Model	Parameter	Estimation (B)	Standard Error (SE)	Wald	Odds Ratio	95% Confidence Interval	
						Lower limit	Upper limit
1	Constant	-0.693	0.612	1.281	0.500	-1.893	0.507
	Difficulty in concentrating	1.386	0.700	3.919	4.000	0.014	2.759
2	Constant	-1.576	0.786	4.021	0.207	-3.117	0.036
	Difficulty in concentrating	1.608	0.755	4.529	4.992	0.127	3.089

Psychomotor agitation	1.371	0.643	4.544	3.941	0.110	2.632
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ASD: autism spectrum disorder.

Discussion

These results show that the individuals in the case group (ASD with hyperactivity) were significantly more likely to have a history of dysarthria and digestive complaints compared to those in the control group (ASD without hyperactivity). There was also a greater likelihood of reported difficulty in concentrating and psychomotor agitation in the case group.

ASD has been associated with different gastrointestinal tract disorders such as irritable bowel syndrome, indigestion, malabsorption, food intolerance, constipation and fecal incontinence (Lázaro, Pondé & Rodrigues, 2016; McKeown, Hisle-Gorman, Eide, Gorman & Nylund 2013). It is possible that the discomfort caused by the gastrointestinal symptoms generates reactive symptoms of hyperactivity bearing in mind the difficulty these children have in expressing their discomfort verbally. In a study conducted by Chaidez, Hansen & Hertz-Picciotto (2014), children with ASD and gastrointestinal complaints had more symptoms of irritability, social isolation, stereotypical behavior and hyperactivity compared to children with no gastrointestinal complaints. There could also be a common etiological pathway involved in the presence of gastrointestinal manifestations and the presence of ADHD symptoms in children with ASD. Since few studies have reported this correlation, it is important for future studies to investigate this hypothesis further.

There were also significantly more reports of dysarthria in the case group compared to the controls, a finding that is in agreement with data from the literature. Cooper, Martin, Langley, Hamshere & Thapar (2014) investigated the clinical characteristics of comorbid ASD/ADHD and found greater language impairment in patients with the comorbidity. Some authors have suggested that ADHD could be associated with phonological abnormalities and with receptive-expressive language disorder (Helland, Posserud, Helland, Heimann & Lundervold, 2016) which would explain the increased speech problems, including the dysarthria reported here in the patients with comorbid ASD/ADHD.

Other differences found between cases and controls were already expected, specifically the greater presence of difficulty in concentrating and psychomotor agitation in the case group, since these are symptoms that are often found together in patients with ADHD. These results are in agreement with other studies in which groups of children with ASD with and without ADHD were evaluated and symptoms of inattention were identified by using questionnaires and/or by clinical observation. Those studies showed that symptoms of inattention were more common and more intense in the group with ASD and ADHD (Andersen et al 2013; Craig et al. 2016; Segenreich & Mattos 2007).

The present study was limited by its small sample size, which precluded the possibility of performing a more sophisticated multivariate analysis. Consequently, some variables that could have been important, such as the presence of verbal language, were left out of the model. Nevertheless, the stringency applied to the diagnostic evaluation and in the definition of the two study groups with and without the symptom of hyperactivity leads us to recommend that further research be conducted into the association between the symptom of hyperactivity in individuals with ASD and gastric problems and greater language impairment.

Conclusion

In conclusion, the present results suggest that the presence of symptoms of hyperactivity in individuals with ASD is associated with differences in their clinical profile, specifically a greater prevalence of digestive complaints, dysarthria, psychomotor agitation and difficulty in concentrating. Further studies may be able to clarify the association between ASD/ADHD and digestive complaints.

Conflict of interest

None.

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