Open Access Scientific Reports

Research Article Open Access

head circumference (HC) in these patients [6,16-19]. Despite this, several studies found no association between PPD and macrocephaly [6,9]. ere is also divergence in whether increased HC is [6,9,15] or is not [10,13,16,18] part of a broader spectrum of macrossomic features. Some investigators have found children with PDD to have a normal HC at birth [4,10,12,18]; others have even to a

Bailey [16] and Lainhart [18] found no association between HC size and cognitive function.

The main objective of our study was to determine whether HC and the growth velocity of HC in children diagnosed with PDD are any different from children without neurodevelopmental disorders, at different age periods.

Patients and Methods

We designed an observational retrospective case-control study with prospective data collection based on the analysis of Head Circumference (HC) measures in 11 periods from birth to 36 months in two groups: 1) a study group of children diagnosed with Pervasive Development Disorder (PDD) by a paediatric consultant based on the criteria outlined by DSM-IV (American Psychiatric Association, 1994) and with a follow-up in an outpatient clinic for development disorders in Hospital de Faro EPE; subjects were excluded for having evidence of a medical condition thought to be associated with PDD; 2) a control group of consecutive children attending general paediatric consultation at the hospital´s outpatient clinic, in which neurodevelopmental disorders were excluded by the attending physician, with at least five HC measures. HC data were collected from medical records (derived from the attending physician) of occipito-frontal circumference measures. The 11 periods considered corresponded to the regular medical consultations recommended by the Portuguese Ministry of number of females with AD and AS, we only included male gender analysis for these two subgroups; female population was only analysed altogether.

In order to minimize possible confounding results regarding differences between groups in birth somatometric parameters, a multivariate regression was performed. Since weeks of gestation and weight at birth were correlated at a significance level of 0.01 (r = 0.733), only the first was included in the logistic regression model.

Within the female population (Figure 1), we found sustained lower values of Head Circumference (HC) in the PDD compared to the control group, and this difference was statistically significant in several periods: birth (p = 0.05) and months 4 (p = 0.03), 6 (p = 0.03), 9 (p = 0.01), 12 (p = 0.02), 15 (p < 0.01) and 18 (p = 0.02).

In the comparative analysis between the total PDD male population and the control male group (Figure 2), we found sustained higher values of HC in the study group, although this was only statistically significant in one period (36 months, p = 0.02).

The autistic disorder group had consistently higher values of HC when compared to the control group (Figure 3), although the differences were not significant in any period.

More consistent results were found for higher values of HC in the AS group compared to the control group (Figure 4), where differences were statistically significant in six periods: months 6 (p < 0.01), 9 (p = 0.01), 12 (p = 0.03), 18 (p = 0.01), 24 (p = 0.02) and 36 (p = 0.02).

In a comparative analysis of HC between AD and AS (Figure 5), although we found a trend for higher values of HC in the latter, differences were not significant except at 6 months (p = 0.03).

With regards to the Growth Velocity (GV) of HC, we found that it was higher for the PDD population (all female PDD, all male PDD, AS and AD) than the control group (Figures 1-5) in the first 6 months of life. Nevertheless, this difference was statistically significant only for AD (p = 0.04). In addition there was a higher GV of HC in AD compared to the control group (p < 0.01) for the periods 6 to 12 months and birth to 36 months. For the remaining periods, there were no significant differences in the GV of HC when comparing the PDD population to the control group and AD to AS.

Discussion

Pervasive Development Disorders (PDD) are thought to be a neurobiological condition, which implies that neurobiological abnormalities must precede the first behavioural expressions. There is evidence from neuropathological data for an evolving pathological process in the brain of children with PDD that extends from the foetal period of brain development into adulthood. Several studies have focused on the brain anatomy of patients with this disorder,

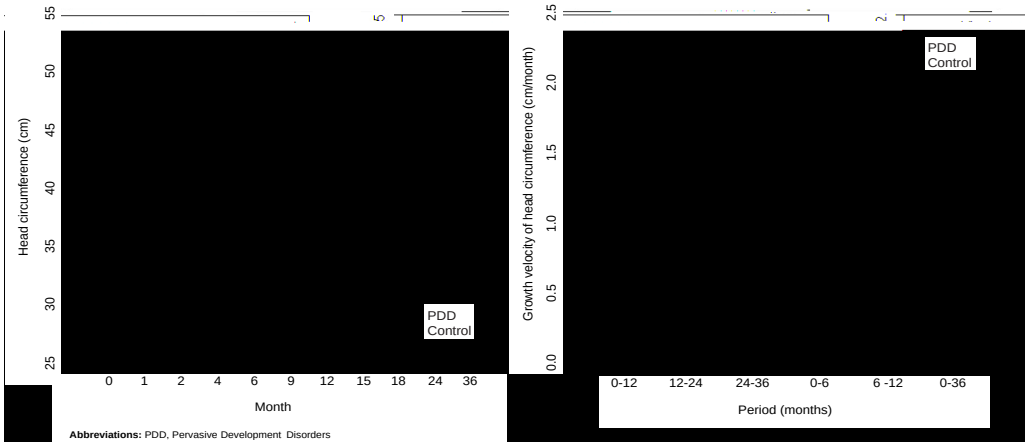


Figure 1: Comparative analysis between girls with Pervasive Development Disorder (PDD) and girls included in control group.

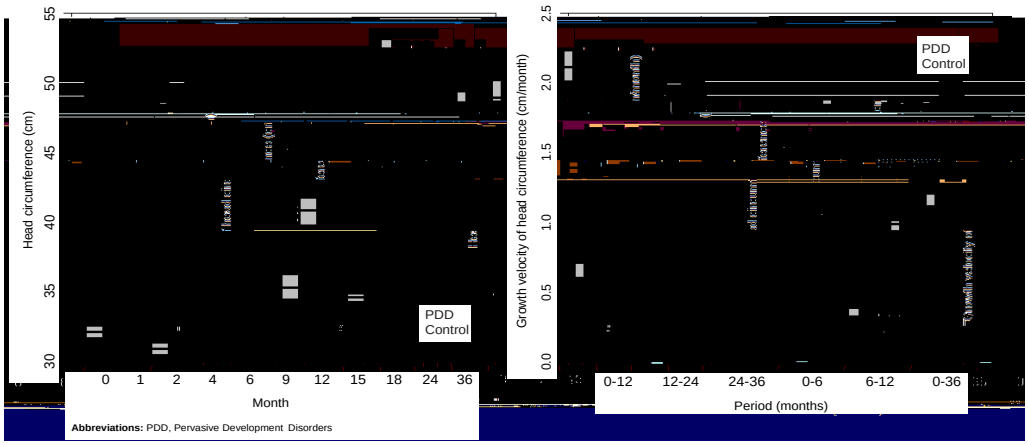


Figure 2: Comparative analysis between boys with Pervasive Development Disorder (PDD) and boys included in control group.

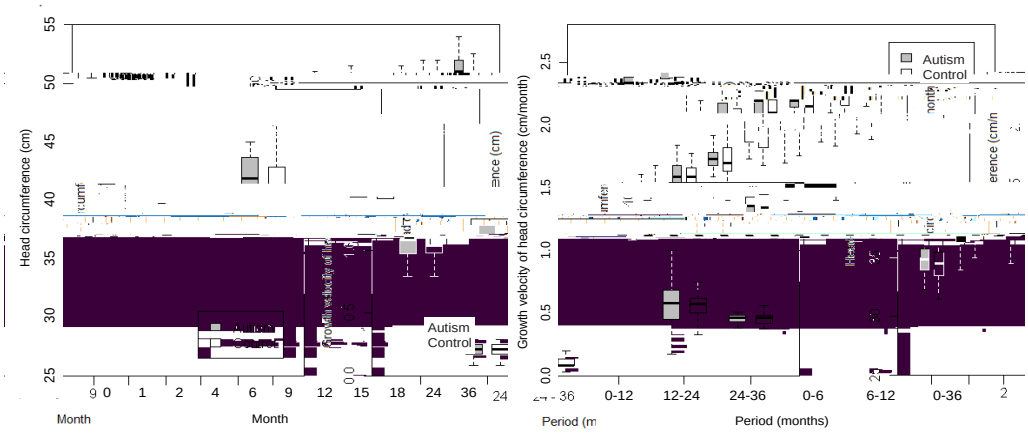
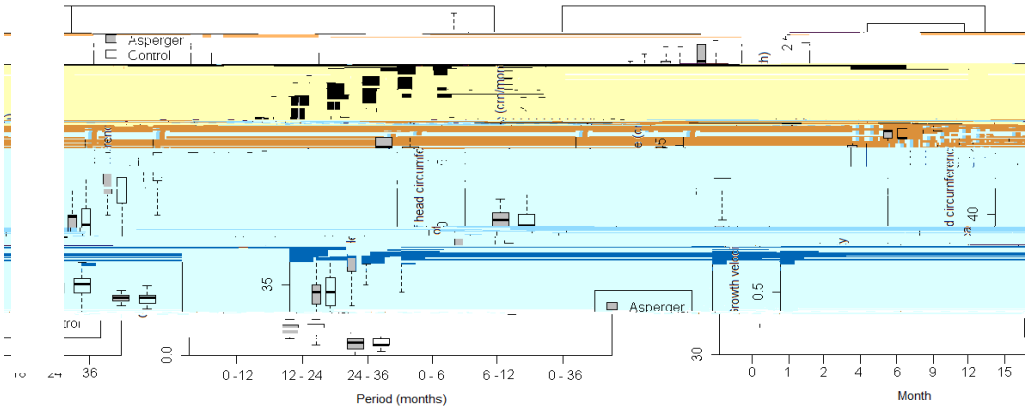


Figure 3: Comparative analysis between boys with autistic disorder and boys included in control group.

based either on imaging (magnetic resonance imaging) or on histological data [10,12]. e results are inconsistent, probably due to the lack of statistical power resulting from small sample sizes, to the heterogeneity of the disorder itself or to the inability to control for potential confounding variables. e most consistent data however concern enlargement of both the grey and white matter volumes of the cerebral cortex [5,10,12] when compared to the control group; cerebellar grey and white matter enlargement has also been indicated



[10]. Other studies have ascertained a higher overall cerebral volume in PDD children compared to healthy ones [5,10,12,13,15]. More pronounced enlargement of the grey matter has been encountered in low functioning Autistic Disorder (AD) compared to other PDD, and has therefore been related to a more severe clinical course [5].

e increase in brain volume could re ect either abnormal acceleration of cerebral growth or a failure of late prenatal and/or early postnatal regressive processes [10]. Gillberg hypothesized that there may be at least two di erent pathways to PDD, one connected with primary temporofrontal dysfunction (and late prenatal/early postnatal origins) and another linked to primary brainstem dysfunction (and early prenatal origins) [14]. e cellular basis of increased brain volume remains unclear and several hypotheses have been postulated: an excessive number or higher rates of growth of neurons and/or glial cells, excessive numbers of minicolumns, excessive and premature expansion of dendritic and axonal arbors, excessive numbers of axonal connections, smaller and more densely packed neurons in the cingulate gyrus and limbic system, premature myelination, and a reduction in the protein levels of the enzymes that synthesize γ-aminobutyric acid and glutamic acid decarboxylase [5,10,14]. e rapid brain overgrowth at an early age that takes place in a critical period of brain development (marked by increases in synaptic connections, dendritic and axonal growth and myelination), must be an important factor in the emergence of characteristic behaviour. In such an important period of development of neuroplasticity and learning, aberrantly rapid and disordered growth without guidance may result in too many connections that may not be adaptive.

e growth of the skull re ects the growth of the brain, and in the absence of gross abnormalities of skull shape, Head Circumference (HC) is a useful index of brain size and brain growth. As in our study, several other authors have used HC measures as a means of evaluation of brain volume.

Within the male population, the higher values of HC obtained at birth in the PDD sample compared to the control group were not statistically di erent, in accordance with several other studies4,10,12,18. In agreement with the literature reviewed, we also found a tendency for higher HC values in PDD in other periods of the rst three years of life, in the male gender [4,6,9,11-19]. is di erence was evident when comparing the control group to PDD in general, to the AD group and to the Asperger Disorder (AS) group. Nevertheless, statistical signi cance was attained in a sustained manner (in six of the 11 periods) only in the comparison between AS and the control group. Like several other authors [5,10], we also found a trend for higher values of HC in AS compared to AD in the rst three years of life, although this di erence was only statistically signi cant in one period (six months).

In the male gender, a trend towards a higher Growth Velocity (GV) of HC in the first six months of life in PDD (PDD in general, AD and AS) was observed, although it was only statistically significant in AD. The growth velocity between six and 12 months and between birth and 36 months was also significantly higher in AD compared to the control group. For all other periods, and considering PDD in general, AD and AS, the growth velocity of HC did not differ significantly when compared to the control group. Likewise, we found no significant differences in the HC rate of growth when comparing AD and AS. This study thus indicates that it is the first six months in the first year of life during which the GV of HC appears to be more pronounced in children with PDD compared to the healthy population.

To our knowledge, our study is the first to compare females

25. Allen DA, Steinberg M, Dunn M, Fein D, Feinstein C, et al. (2001) Autistic disorder versus other pervasive developmental disorders in young children: same or different? Eur Child Adolesc Psychiatry 10: 67-78.

26. Ehlers S, Gillberg C, Wing L (1999) A screening questionnaire for Asperger syndrome and other high-functioning autism spectrum disorders in school age children. J Autism Dev Disord 29: 129-141.

27. Myhr G (1998) Autism and other pervasive developmental disorders: exploring the dimensional view. Can J Psychiatry 43: 589-595.

28. Walker DR, Thompson A, Zwaigenbaum L, Goldberg J, Bryson SE, et al. (2004) Specifying PDD-NOS: a comparison of PDD-NOS, Asperger syndrome, and autism. J Am Acad Child Adolesc Psychiatry 43: 172-180.

29. Ayuda-Pascual R, Martos-Pérez J (2007) [The influence of the social perception of emotions in the formal language of children with Asperger's syndrome or high-functioning autism]. Rev Neurol 44 Suppl 2: S57-59.

30. Cox AD (1991) Is Asperger's syndrome a useful diagnosis? Arch Dis Child 66: 259-262.

31. Hill EL, Frith U (2003) Understanding autism: insights from mind and brain. Philos Trans R Soc Lond B Biol Sci 358: 281-289.

32. Belinchón-Carmona M, Posada-De la Paz M, Artigas-Pallarés J, (2005) Guía de buornos del espectro autista. Rev Neurol 41: 371-377.

33. Poirier N, Forget J (1998) [Diagnostic criteria of autism and Asperger's syndrome: similarities and differences]. Sante Ment Que 23: 130-148.

34. Ayuda-Pascual R, Martos-Pérez J (2007) [The influence of the social perception of emotions in the formal language of children with Asperger's syndrome or high-functioning autism]. Rev Neurol 44 Suppl 2: S57-59.

35. http://www.R-project.org