Is megalencephaly specific to autism?

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Abstract

Several recent reports have described the presence of increased head circumference (megalencephaly) in patients with autism. Although some studies have described reports of megalencephaly in other disorders such as schizophrenia in adults, few such studies have been performed in children and adolescents. In the present study, the authors compared 20 subjects with autism/pervasive developmental disorder (DSM-IV; all males; mean age = 10.9 years) with 20 controls with attention deficit hyperactivity disorder (DSM-IV; all males; mean age = 11.1 years). Four subjects and five controls had evidence of megalencephaly. In addition to their core symptoms, the autistic subjects with megalencephaly were hyperactive and impulsive. These findings suggest that megalencephaly may not be specific to autism, and when present, it may index the presence of additional symptoms such as hyperactivity and impulsivity.

Keywords autism, hyperactivity, impulsivity, megalencephaly

Introduction

Megalencephaly is a term used to denote an abnormal increase in brain size which could be either anatomic (e.g. neurofibromatosis and cerebral gigantism), metabolic (e.g. storage diseases) or idiopathic. In clinical practice, this condition is estimated by measuring the head circumference [occipitofrontal circumference (OFC)]. Patients with a head circumference over two standard deviations above the mean (ninety-eighth percentile) for age are said to have megalencephaly. About one out of every 50 (2%) children in the general population may have megalencephaly (Sandler et al. 1997).

Among the neuropsychiatric disorders of childhood, an association has been proposed between megalencephaly and autism, a severe developmental disorder characterized by reciprocal social deficits, communication deficits and rigid ritualistic interests, first described by Kanner (1943), and now classified as the main category in the group of pervasive developmental disorders (PDDs). Several recent reports have drawn attention to the presence of increased head circumference in autism, an observation first made by Kanner (1943) himself. For example, Woodhouse et al. (1996) compared children with PDDs with a control group of children with other (axis one) psychiatric disorders. Eleven (29%) out of 37 patients with PDDs had a head circumference greater than the ninety-seventh percentile, while five (17%) out of the 30 with other axis one disorders had a head circumference in the ninety-seventh percentile. Details about the various axis one disorders were not given. Another study (Lainhart et al. 1997) investigated the occurrence of megalencephaly in a group 91 subjects with autism. Thirteen (14.3%) of the 91 subjects had head circumferences above the ninety-seventh percentile. No relationship was found between megalencephaly
and any of the clinical features assessed. No control group was used to determine how specific this feature was to autism (Lainhart et al. 1997). Data from imaging studies (Piven et al. 1995) and post-mortem studies in autism (Bauman & Kemper 1994) have also suggested that head circumference may be increased in autism.

However, research in adult psychiatric patients has demonstrated that increased head circumference may occur in a wide range of disorders such as schizophrenia and Alzheimer's disease (Bassett et al. 1996; Katzman et al. 1988). To the present authors' knowledge, similar comparative studies have not been undertaken in children with psychiatric disorders. In order to investigate this issue, they examined a group of children with autism/PDDs and compared them with a control group of children with attention deficit hyperactivity disorder (ADHD). The main purpose of the present study was to investigate the specificity of megalencephaly in autism and to determine the extent to which it occurs in other neuropsychiatric disorders of childhood.

Method

The present study was conducted at the University of Michigan Medical Center, Ann Arbor, MI, USA. Consecutive patients with pervasive developmental disorder referred to the Developmental Disorders Clinic and a community mental health centre were recruited prospectively. The diagnosis of pervasive PDDs, in which autistic disorder was the main category, was based on the DSM-IV (APA 1994) and consisted of the following process: a detailed developmental history, an autism behaviour checklist (Krug et al. 1980) completed by the primary caregiver, speech and language evaluation, psychological testing, and educational behavioural assessment. Measurement of head circumference was done by placing a measuring tape over the eyebrows and passing it around the head to fit snugly over the most posterior protuberance of the occiput (Cameron 1978). In order to establish reliability, 10 subjects were randomly examined by one of the investigators (J.Z.); another investigator (M.G.) subsequently examined the same 10 subjects. Agreement was found in nine subjects; in the tenth subject, the difference noted was corrected by joint measurement. In another set of 10 subjects, another investigator (S.E.) performed the measurements which were all subsequently repeated by M.G. with total agreement. The controls consisted of patients with a diagnosis of ADHD based on the DSM-IV (APA 1994) and supplemented with a score of at least 20 on the Conners’ Parent-Teacher Questionnaire. Children with ADHD were chosen as controls because, like autism, ADHD is a childhood onset disorder which often results in social deficits because of impulsivity and hyperactivity. All the controls had to suffer from symptoms of ADHD at the time of the present study and were on medications and/or behaviour treatment. In order to minimize the effect of sex, only male subjects were included. Subjects were matched as close as possible to their age. The assessment of the presence of intellectual disability (mental retardation) was done on the basis of a full-scale IQ < 70 or on clinical grounds (based on information about levels of self-care and adaptive functioning). Twenty patients were recruited in each group: (PDDs) mean age (± SD) = 10.9 ± 3.9 years, 13 subjects with intellectual disability; and (ADHD) mean age (± SD) = 11.1 ± 3.7 years, six subjects with intellectual disability.

Results

Out of a total of 40 subjects, nine patients had an increased head circumference (two standard deviations over the mean) (Table 1). Out of these subjects, four patients had autism/PDDs and five had ADHD. Subjects with increased head size were not more likely to have an increased history of intellectual disability or seizure disorder. One, 12-year-old subject had a diagnosis of Asperger syndrome and Tourette syndrome; the remaining three patients, aged 10, 6 and 4 years, had intellectual disability and autistic disorder. All the subjects with PDDs and increased head circumference had marked hyperactivity and impulsivity as their presenting symptoms, and two out of the four subjects were on medication to control these symptoms.

Discussion

The present study showed that about 20% of the PDDs sample had megalencephaly, which is broadly
consistent with the rate of 25–30% reported in other studies (Woodhouse et al. 1996). However, an equal number of patients with ADHD also had an increased head circumference and the differences between the two groups were not significant. When patients with PDDs and megalencephaly were re-examined, all of them had hyperactivity as a major presenting symptom. Two out of the four patients with megalencephaly and autism were on medications for the treatment of hyperactivity and impulsivity. This raises the possibility that megalencephaly may not be specific to autism, and that it may index additional symptoms such as hyperactivity and impulsivity when present. Indeed, hyperactivity and attentional problems have been described in patients with megalencephaly. For example, Sandler et al. (1997) compared 20 children with megalencephaly, aged 5–15 years, with their siblings and controls. Patients with megalencephaly scored higher on the Conners' scales for hyperactivity and impulsivity compared with the controls and their siblings, although the differences did not reach statistical significance. However, the present authors did not clarify if any of their cases suffered from comorbid autism. Smith et al. (1984) studied a group of children enrolled in special education classrooms. The children were required to have no known physical handicap, a full-scale IQ $\geq 80$, and the presence of significant impairment in areas of auditory, visual and visuomotor processing. Seventy-five children between the ages of 6 and 13 years were compared with a control group of 73 children in regular classrooms. The former group was found to have more children with megalencephaly (OFC head circumference of two or more standard deviations above the mean) than the control group. While individual psychiatric diagnoses of the children in special education were not given, this group included children with deficits in attention and motor output, and probably included patients with ADHD, although this was not clearly stated.

Megalencephaly has also been described in some other neurodevelopmental disorders in adults such as schizophrenia. For example, in a study of 100 chronic inpatients with a DSM-III-R diagnosis of chronic schizophrenia or schizo-affective disorder, Bassett et al. (1996) found an excess of male patients with a larger than expected head circumference for height; one out of every six males had relative megalencephaly. The above authors suggested that the observed increase in head size in their sample might have been caused by overgrowth, secondary to pleitropic expression of a developmental gene, or some other unknown acquired factors (Bassett et al. 1996). Increased head size has also been noted in some patients with Alzheimer disease. Some authors have suggested that increased head size in Alzheimer disease may offer some degree of protection against the illness. Katzman et al. (1988) studied a group of 10 elderly patients with neuropathologically diagnosed Alzheimer disease and preserved mental functions during life time. The above authors proposed that these patients may have started life with a larger brain volume and larger neurones which may have provided them with an additional reserve. Although these studies were done in adults, the material questions the specificity of megalencephaly in psychiatric disorders. Another point which should be noted is that megalencephaly tends to cluster in families in both normal as well as in neurologically impaired subjects. Hanssen et al. (1993) described a large family with Cowden disease, a disorder characterized by megalencephaly, intellectual disability and multiple hamartoma formation. Affected individuals with a large four-generation family were described. Megalencephaly was noted in all affected individuals and was
markedly progressive in three out of six affected children of the fourth generation.

Although megalencephaly may not be specific to autism, discrete groups of patients with autism and megalencephaly may occur within the PDDs group, raising several issues which need to be investigated. Firstly, it is not clear if megalencephaly is present since birth. For example, Orstavik et al. (1997) described two sisters who had autism with macrocephaly, seizure disorder, intellectual disability, and social and communication deficits typical of autism (e.g. echolalia). Neither subject had macrocephaly at birth; the first sister had an OFC of 36 cm (seventy-fifth percentile) at birth: ‘head size increased rapidly after birth, but after 6 months, the OFC remained stable at 23 cm above the ninetieth percentile’ (p. 849). The second sister had an OFC of 34 cm (twenty-fifth percentile) at birth. However, she also ‘developed macrocephaly with OFC 2 cm above the 97.5th centile from the age of 6 months’ (p. 849). Both patients had normal head size at birth which gradually increased later on during infancy. It has not been proven if this is true of all cases of autism with macrocephaly and the matter needs to be investigated systematically. Secondly, it is worth investigating if spontaneous attenuation in this feature can occur over time. For example, in some cases of leukodystrophy, a condition associated with macrocephaly, spontaneous attenuation of white matter changes occurs over time (Robinson & Cox 1997). Furthermore, it is unclear if the brain enlargement seen in some patients with autism is localized or generalized, or if it is associated with family/clinical features. The present study was based on a modest number of cases and was derived from a clinic sample which may not be representative of the larger population of PDDs and ADHD children. Despite these limitations, the findings cast doubt on the specificity of megalencephaly in autism, while recognizing that a subgroup of autistic children may have an increased head circumference. Thus, more research is needed into the causes and correlates of megalencephaly in autism and related disorders.

References


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