Neurodevelopmental disorders in children with macrocephaly: A prevalence study and PTEN gene analysis

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Abstract

Purpose: To clarify the relationship between macrocephaly and neurodevelopmental disorders, as well as identify the prevalence of PTEN mutations in autism spectrum disorders with macrocephaly in Japan.

Subjects and methods: Diagnostic and other medical information of children with macrocephaly younger than 4 years (n = 93) were collected for analysis. PTEN gene mutation analysis was conducted in another set of 16 macrocephalic individuals aged 3–22 years.

Results: Sixteen macrocephalic children were associated with neurodevelopmental disorders, including autism spectrum disorders (ASDs) (n = 6), autistic traits (n = 5), intellectual disability (n = 5), attention deficit hyperactivity disorder (n = 1), developmental coordination disorders (n = 1), and language disorder (n = 1). Male gender was significantly linked to these disorders, whereas a family history and degree of macrocephaly were not significantly linked to the diagnosis. A novel mutation in the PTEN gene was identified in a 16-year-old girl with autism, mental retardation, language delay, extreme macrocephaly (+4.7 SD) with a prominent forehead, and digital minor anomalies.

Conclusion: Children with macrocephaly, particularly males, are at a higher risk of neurodevelopmental disorders, rather than progressive etiologies, such as hydrocephalus and neurodegenerative disorders. The data provide a basis for routine health checks for young children in Japan, including the follow-up management and possible screening of PTEN mutations in children with ASDs and macrocephaly.

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1. Introduction

Macrocephaly in young children has been classically considered a risk factor for serious neurological diseases, including hydrocephalus accompanying brain tumors, leukodystrophies, and other neurodegenerative diseases such as GM2 gangliosidosis. Additionally, some reports revealed that macrocephaly is a biomarker of the
autism spectrum disorders (ASDs), reported in 12–31% of autistic children [1–4]. In turn, approximately 3% of boys with macrocephaly were associated with ASDs [5]. The proportion of ASDs in children with macrocephaly, irrespective of their sex, or in populations outside England, has not been reported.

Multiple genetic factors have been identified to cause ASDs [6–8]. Among others, mutations in the PTEN (phosphatase and tensin homolog) gene have been identified in individuals with autism accompanied by macrocephaly [9–11], which account for 1%–17% of ASDs with macrocephaly [9,10]. The protein encoded by PTEN gene was initially recognized as a tumor suppressor, which antagonizes the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway and suppresses the proliferation of cancer cells through inhibition of the mammalian target of rapamycin (mTOR) pathway downstream of AKT [12]. Tuberous sclerosis complex (TSC) is caused by the activation of the mTOR pathway due to TSC1/2 mutations, and up to 50% of children with TSC manifest with ASDs [13]. mTOR inhibitors, such as rapamycin, can recover the impaired social interaction in TSC2+/− mice with simultaneous reduction of elevated phospho-S6K levels in the brain [14]. Furthermore, they can ameliorate autistic symptoms in adolescents with TSC [15] as well as abnormal behaviors in Pten knockout mice [16]. Thus, these agents may be potentially effective for the treatment of autistic children with macrocephaly due to PTEN mutations.

With this background, our first aim was to confirm the correlation between macrocephaly and ASDs and their proportions in Japanese children to assist in diagnosis during health visits and to provide information for medical follow-up based on early intervention. Our second aim in this study was to determine the prevalence of children with macrocephaly associated with PTEN mutations in Japan to develop increased understanding for preparing a screening plan for the future.

2. Subjects and methods

2.1. Prevalence of neurodevelopmental disorders in macrocephalic children

This study enrolled 93 Japanese children with macrocephaly, aged 1–44 months, who were referred to the Division of Child Neurology, Tottori University Hospital between January 2006 and August 2015. Two subjects already diagnosed with congenital hydrocephalus and megalencephalic leukoencephalopathy with subcortical cysts, confirmed before the initial referral, were excluded before enrollment. We defined macrocephaly as an occipito-frontal head circumference (HC) above 2 standard deviations (SD) from the mean for age. Each subject was examined by experienced child neurologists to diagnosis developmental disorders. Diagnoses were initially based on DSM-IV criteria and were converted to the classification in DSM-V for description in this study, with diagnoses of pervasive developmental disorder and mental retardation converted to ASDs and intellectual disability (ID), respectively. An initial diagnosis of Asperger syndrome was converted to ASDs in several cases. Subjects who were suspected to have ASDs and had the potential for social impairment, but definite diagnosis was withheld due to young age as well as those who did not completely meet the contents of criterion A in the DSM-V diagnostic criteria for ASDs were classified as having “autistic traits.” ID was defined by an intelligence quotient (IQ) score or developmental quotient (DQ) below 70. IQ/DQ was determined based on the results of the Wechsler Intelligence Scale for Children-Fourth Edition, revised version of the Kyoto Scale of Psychological Development, Kinder infant development scale, or Enjoji developmental scale. Information on the family history of macrocephaly, accompanying conditions, and the imaging findings of cranial computed tomography (CT) or the brain magnetic resonance imaging (MRI) were also collected. The study design was approved by the ethical committee of the Tottori University Faculty of Medicine.

2.2. PTEN mutation analysis

The macrocephalic subjects with ASDs and/or ID who were referred to our department between 2004 and 2012 (16 subjects with ASDs (n = 15)/autistic traits (n = 1)) were enrolled into this study after having written informed consent from their parents. Three subjects with ASDs/autistic traits in the prevalence study were also included in this study. For the genetic diagnosis, blood samples were obtained from the patients, parents, and siblings after written informed consent was obtained from the parents. Genomic DNA was extracted from the blood samples using a standard protocol. All nine exons and exon–intron junctions of the PTEN gene were amplified from genomic DNA by PCR using primers designed with primer software (Genetyx software, Genetyx, Shibuya, Japan). The primers were designed to include an intron of 50 bp surrounding the exon. The sequencing was performed using forward and reverse primers. All the primer sequences are available on request. Sequencing was performed with a BigDye Terminator v3.1 Cycle Sequencing Kit and a 3500× L Genetic Analyzer capillary sequencer (Life Technologies, Carlsbad, CA, USA). Publicly available prediction programs, such as PolyPhen-2 and SIFT algorithm, were used to analyze the detected variants [17,18]. The study design was approved by the ethical committee of the Tottori University Faculty of Medicine.
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