Infantile Cerebellar Pilocytic Astrocytoma with Autism Spectrum Disorder

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Abstract

The etiology of autism remains unclear, but relationships to cerebellar factors have been reported. We report 2 cases of infantile cerebellar pilocytic astrocytoma in children with autism spectrum disorder. Cerebellar tumors may be related to the pathogenesis of autism. (J Nippon Med Sch 2012; 79: 228–231)

Key words: infantile pilocytic astrocytoma, autism, autism spectrum disorder

Introduction

Autism is a type of neurodevelopmental disorder involving retardation of socialization and communication abilities. The underlying cause remains largely unknown, but a close relationship may exist between autism and cerebellar lesions, with some authors reporting autistic patients with cerebellar lesions. We report herein 2 cases of cerebellar pilocytic astrocytoma arising in children with autism spectrum disorder (ASD).

Case Reports

Case 1

A 5-year-old boy was referred to our hospital because of gait disturbance. He had a history of autism diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR)¹, and his intelligence quotient (IQ) was 69 on admission. Physical

examination revealed a head circumference of 55 cm. Neurological examination detected cerebellar ataxia and dysmetria. Papilledema was evident bilaterally. Computed tomography (CT) of the head showed a cerebellar cyst associated with a nodular tumor and obstructive hydrocephalus. Magnetic resonance imaging (MRI) disclosed strong, homogenous enhancement of the tumor with no enhancement of the cyst wall (**Fig. 1A**). The tumor was removed surgically, and histopathological examination confirmed pilocytic astrocytoma (**Fig. 2A**). Cerebellar signs and papilledema resolved postoperatively, but the IQ and autistic behaviors remained unchanged.

Case 2

A 6-year-old girl was brought to the hospital because of headache. Asperger syndrome was diagnosed according to DSM-IV-TR, and the IQ was 92 on admission. A family history of ASD was identified. Her 15-year-old brother had received a diagnosis of autism, and her 39-year-old father had high-functioning autism. Autism-spectrum quotients²

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Fig. 1

A) Case 1

Magnetic resonance image (A1) and computed tomogram (A2) for a 5-year-old boy who presented with gait disturbance show an enhancing nodule with a large cyst in the cerebellum. Obstructive hydrocephalus and thinning of the occipital bone are observed.

B) Case 2

Magnetic resonance image of a 6-year-old girl showing a partially enhancing mural nodule with a peritumoral cyst in the cerebellar vermis.

Fig. 2

A) Case 1

Vacuolated cells with small, round nuclei are present in the spongy area. A Rosenthal fiber is apparent. (H & E, $\times 40$)

B) Case 2

Cells with small nuclei showing microcysts. Eosinophilic granular bodies are observed. Tumor cells are positive for glial fibrillary acidic protein (not shown). (H & E, $\times 40$)

in these family members were 42 and 34, respectively. The patient showed no neurological deficits. Both CT and MRI showed a partially enhancing nodule and cyst in the cerebellar vermis (**Fig. 1B**). No abnormalities other than the vermis lesion were identified. She underwent surgery, and the nodule was totally resected. The histological diagnosis was pilocytic astrocytoma (**Fig. 2B**). Postoperatively, headache resolved completely, but the ASD remained unchanged.

Discussion

Autism is a neurodevelopmental disorder mainly affecting children which is characterized by language problems and communication deficits. Impaired social interactions, lack of communication skills and restricted and repetitive behaviors are key symptoms. ASD is a clinical entity that includes autism and the wide variety of conditions between

“normal” and autism.

ASD includes classical autism, Asperger syndrome, and pervasive developmental disorder not otherwise specified and is diagnosed according to the criteria of DSM-IV-TR¹. Autism spectrum index is also used to diagnose ASD, and the cut-off value for discriminating ASD from normal is 33^{2,3}.

The etiology of ASD remains unclear, but strong relationships have been documented with such factors as genetic disorders (tuberous sclerosis⁴, neurofibromatosis⁵, and fragile X syndrome⁶), metabolic disorders (phenylketouria⁷ and Lesch-Nyhan syndrome⁸), brain anomalies (congenital hydrocephalus⁹), infections (rubellavirus, cytomegalovirus, and influenzavirus)¹⁰⁻¹³, drug-induced disorders (antiepileptic agents¹⁴, alcohol¹⁵, and thalidomide¹⁶), and perinatal disorders¹⁷. ASD sometimes shows physical abnormalities, such as macrocephaly¹⁸, and high blood serotonin levels¹⁹.

Cerebellar and brainstem hypoplasia, abnormality of the corpus callosum, and volume reduction of the cingulate gyrus have also been associated with ASD²⁰. These changes have been observed during fetal development^{21,22}. Other authors have reported that autism is probably caused by brain tumors and brain injuries²³⁻²⁵.

In children, congenital hypoplasia of the cerebellum (particularly the vermis) is reportedly often accompanied by a wide range of neurodevelopmental disorders²⁶⁻²⁹. Other reports on the relationship between autism and cerebellar lesions have noted low numbers of Purkinje cells^{30,31}, reductions in Purkinje cell size³², and dysregulation of Reelin and Bcl-2 proteins, which are related to Purkinje cell migration³³. Studies of astrocytomas of the posterior fossa have revealed the presence of cognitive deficits after tumor removal³⁴. ASD thus does not appear as a functional disease, but rather as an organic disorder. A relationship may exist between autism and the cerebellum.

Autism may not be a symptom resulting from tumor compression, because no changes were seen in our cases after the removal operations. Furthermore, we observed no postoperative exacerbation of autistic symptoms. No evidence of histological changes to the normal cerebellum was

apparent in our cases, but we removed only neoplastic lesions and did not analyze normal tissue. Histopathological characteristics in these cases were representative of typical cerebellar pilocytic astrocytoma.

Pilocytic astrocytoma is World Health Organization grade I tumor, is characterized by slow progression, and may be a congenital tumor when found in children, as in the present cases. There may be a relationship between ASD and infantile cerebellar pilocytic astrocytoma.

References

1. American Psychiatric Association, Task Force on DSM-IV: Diagnostic and statistical manual of mental disorders:DSM-IV-TR, 4th ed, 2000; American Psychiatric Association, Washington DC.
2. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E: The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J Autism Dev Disord* 2001; 31: 5-17.
3. Wakabayashi A, Baron-Cohen S, Wheelwright S, Tojo Y: The autism-spectrum quotient (AQ) in Japan: a cross-cultural comparison. *J Autism Dev Disord* 2006; 36: 263-270.
4. Lawlor BA, Maurer RG: Tuberous sclerosis and the autistic syndrome. *Br J Psychiatry* 1987; 150: 396-397.
5. Mouridsen SE, Andersen LB, Sørensen SA, Rich B, Isager T: Neurofibromatosis in infantile autism and other types of childhood psychoses. *Acta Paedopsychiatr* 1992; 55: 15-18.
6. Brown WT, Friedman E, Jenkins EC, et al: Association of fragile X syndrome with autism. *Lancet* 1982; 1: 100.
7. Miladi N, Larnaout A, Kaabachi N, Helayem M, Ben Hamida M: Phenylketonuria: an underlying etiology of autistic syndrome. a case report. *J Child Neurol* 1992; 7: 22-23.
8. Money J: New phylism theory and autism: pathognomonic impairment of troopbonding. *Med Hypotheses* 1983; 11: 245-250.
9. Fernell E, Gillberg C, von Wendt L: Autistic symptoms in children with infantile hydrocephalus. *Acta Paediatr Scand* 1991; 80: 451-457.
10. Libbey JE, Sweeten TL, McMahon WM, Fujinami RS: Autistic disorder and viral infections. *J Neurovirol* 2005; 11: 1-10.
11. Markowitz PI: Autism in a child with congenital cytomegalovirus infection. *J Autism Dev Disord* 1983; 13: 249-253.
12. Riva D: The cerebellar contribution to language and sequential functions: evidence from a child with cerebellitis. *Cortex* 1998; 34: 279-287.
13. Shi L, Fatemi SH, Sidwell RW, Patterson PH: Maternal influenza infection causes marked behavioral and pharmacological changes in the

- offspring. *J Neurosci* 2003; 23: 297–302.
14. Rasalam AD, Hailey H, Williams JH, et al: Characteristics of fetal anticonvulsant syndrome associated autistic disorder. *Dev Med Child Neurol* 2005; 47: 551–555.
15. Harris SR, MacKay LL, Osborn JA: Autistic behaviors in offspring of mothers abusing alcohol and other drugs: a series of case reports. *Alcohol Clin Exp Res* 1995; 19: 660–665.
16. Dufour-Rainfray D, Vourc'h P, Tourlet S, Guilloteau D, Chalon S, Andres CR: Fetal exposure to teratogens: evidence of genes involved in autism. *Neurosci Biobehav Rev* 2011; 35: 1254–1255.
17. Mason-Brothers A, Ritvo ER, Guze V, et al: Pre-, peri-, and postnatal factors in 181 autistic patients from single and multiple incidence families. *J Am Acad Child Adolesc Psychiatry* 1987; 26: 39–42.
18. Fidler DJ, Bailey JN, Smalley SL: Macrocephaly in autism and other pervasive developmental disorders. *Dev Med Child Neurol* 2000; 42: 737–740.
19. Hanley HG, Stahl SM, Freedman DX: Hyperserotonemia and amine metabolites in autistic and retarded children. *Arch Gen Psychiatry* 1977; 34: 521–531.
20. Casanova MF, Buxhoeveden DP, Switala AE, Roy E: Minicolumnar pathology in autism. *Neurology* 2002; 58: 428–433.
21. Casanova MF, Buxhoeveden D, Gomez J: Disruption in the inhibitory architecture of the cell minicolumn: implications for autism. *Neuroscientist* 2003; 9: 496–507.
22. Casanova MF, van Kooten IA, Switala AE, et al: Minicolumnar abnormalities in autism. *Acta Neuropathol (Berl)* 2006; 112: 287–303.
23. Levisohn L, Cronin-Golomb A, Schmahmann JD: Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. *Brain* 2000; 123: 1041–1050.
24. Riva D, Giorgi C: The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. *Brain* 2000; 123: 1051–1061.
25. Schmahmann JD: Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *J Neuropsychiatry Clin Neurosci* 2004; 16: 367–378.
26. Courchesne E, Yeung-Courchesne R, Press GA, Hesselink JR, Jernigan TL: Hypoplasia of cerebellar vermal lobules VI and VII in autism. *N Engl J Med* 1988; 318: 1349–1354.
27. Hashimoto T, Tayama M, Miyazaki M, Murakawa K, Kuroda Y: Brainstem and cerebellar vermis involvement in autistic children. *J Child Neurol* 1993; 8: 149–153.
28. Hodge SM, Makris N, Kennedy DN, et al: Cerebellum, language, and cognition in autism and specific language impairment. *J Autism Dev Disord* 2010; 40: 300–316.
29. Piven J, Arndt S: The cerebellum and autism. *Neurology* 1995; 45: 398–402.
30. Bauman ML, Kemper TL: Neuroanatomic observations of the brain in autism: a review and future directions. *Int J Dev Neurosci* 2005; 23: 183–187.
31. Ritvo ER, Freeman BJ, Scheibel AB, et al: Lower Purkinje cell counts in the cerebella of four autistic subjects: initial findings of the UCLA-NSAC Autopsy Research Report. *Am J Psychiatry* 1986; 143: 862–866.
32. Fatemi SH, Halt AR, Realmuto G, et al: Purkinje cell size is reduced in cerebellum of patients with autism. *Cell Mol Neurobiol* 2002; 22: 171–175.
33. Fatemi SH, Stary JM, Halt AR, Realmuto GR: Dysregulation of Reelin and Bcl-2 proteins in autistic cerebellum. *J Autism Dev Disord* 2001; 31: 529–535.
34. Riva D, Pantaleoni C, Milani N, Fossati Belani F: Impairment of neuropsychological functions in children with medulloblastomas and astrocytomas in the posterior fossa. *Childs Nerv Syst* 1989; 5: 107–110.

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