Nationwide Survey of the Etiology and Associated Conditions of Prenatally and Postnatally Diagnosed Congenital Hydrocephalus in Japan

Kouzo MORITAKE, Hidemasa NAGAI, Takeshi MIYAZAKI, Noriko NAGASAKO, Mami YAMASAKI*, and Akiko TAMAKOSHI**

Department of Neurosurgery, Shimane University School of Medicine, Izumo, Shimane; *Department of Neurosurgery and Clinical Institute, Osaka National Hospital, National Hospital Organization, Osaka; **Medical Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Nagoya, Aichi

Abstract

A nationwide survey in 2000 investigated the causative and associated central nervous system (CNS) lesions of congenital hydrocephalus in Japan. The etiology and associated diseases in 393 patients with congenital hydrocephalus were analyzed and compared between 193 patients with prenatally diagnosed (fetal) hydrocephalus and 181 with postnatally diagnosed (infantile) hydrocephalus. Of 393 patients of congenital hydrocephalus, 355 (90.3%) had primary hydrocephalus and 28 (7.1%) had secondary hydrocephalus. Of 355 patients with primary hydrocephalus, 85 (23.9%) had simple hydrocephalus associated with no other CNS anomaly and 270 (76.1%) had complicated hydrocephalus associated with other CNS anomalies. Destructive cystic lesions, holoprosencephaly, and agenesis of the corpus callosum were significantly predominant in fetal hydrocephalus. Arachnoid cyst was somewhat predominant in infantile hydrocephalus. The majority of cases of congenital hydrocephalus were primary hydrocephalus and two thirds were complicated hydrocephalus. Several complications showed marked predominance in fetal hydrocephalus.

Key words: congenital hydrocephalus, fetal hydrocephalus, etiology, nationwide survey, Japan

Introduction

Hydrocephalus involves an abnormal increase in the volume of cerebrospinal fluid manifesting primarily as enlargement of the ventricles, and may be associated with cerebral atrophy and mental retardation. Computed tomography, ultrasonography, magnetic resonance (MR) imaging, and other supplementary techniques now allow observation of the evolution and progression of hydrocephalus from the earliest to the final stages. Consequently, the concept and classification of hydrocephalus have changed.

The prevalence of hydrocephalus is reported to be 0.82 per 1000 live births, 0.49 for children with infantile hydrocephalus and 0.33 for children with meningomyelocele. The etiology was prenatal in 55% and perinatal in 44% of children with infantile hydrocephalus. The most common congenital and acquired causes of hydrocephalus are reported to be spina bifida, aqueductal stenosis, and premature birth with low weight in infancy with ventricular hemorrhage.

The present study investigated the etiology and associated diseases of congenital hydrocephalus in Japan in cases diagnosed prenatally (fetal hydrocephalus) and postnatally (infantile hydrocephalus).

Materials and Methods

A nationwide survey of congenital hydrocephalus in Japan was carried out in 2000 under the sponsorship of the Ministry of Health, Labor and Welfare of Japan. An initial postcard questionnaire was sent in January 2000 to 2440 departments of pediatrics, neurosurgery, or obstetrics and gynecology in Japan. Congenital hydrocephalus was defined as increased retention of cerebrospinal fluid in the ventricles associated with ventricular dilation diagnosed up to 12 months after birth. This asked about the number of patients with hydrocephalus who had visited the...
outpatient clinics or had been hospitalized between January 1 and December 31, 1999. Individual questionnaires, asking for epidemiological and clinical details, were sent to the 1861 departments (76.3%) that had replied to the first survey.

The prevalence of congenital hydrocephalus varies substantially depending on the inclusion criteria of the study.14) In this study, hydrocephalus was classified by etiology into two groups, primary hydrocephalus caused by developmental disorders and secondary hydrocephalus caused by non-developmental insults, such as hemorrhage, tumor, or infection.3) Primary hydrocephalus was further classified into simple hydrocephalus (isolated hydrocephalus14)) with no other concomitant central nervous system (CNS) anomaly except for aqueduct stenosis, and complicated hydrocephalus with other complicating CNS anomalies.

A total of 393 patients with congenital hydrocephalus were identified, 193 with fetal hydrocephalus, 181 with infantile hydrocephalus, and 19 with unspecified hydrocephalus diagnosed at an unknown time. The etiology of hydrocephalus and other pathologic conditions was analyzed in each of the patients with congenital hydrocephalus, and were compared between the fetal hydrocephalus and infantile hydrocephalus groups. All personal data items were subjected to privacy protection.

Statistical analysis used the chi-squared ($\chi^2$) test and Kruskal-Wallis H test, and were conducted with Excel 2004 (version 11.2.3; Microsoft, Redmond, Wash., U.S.A.) and SPSS (version 8.0 for Windows; SPSS, Chicago, Ill., U.S.A.) with significance accepted at the 5% level.

Table 2 Patients with secondary congenital hydrocephalus

<table>
<thead>
<tr>
<th>Cause of secondary congenital hydrocephalus</th>
<th>Fetal hydrocephalus</th>
<th>Infantile hydrocephalus</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>10</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Tumor</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15</strong></td>
<td><strong>13</strong></td>
<td><strong>28</strong></td>
</tr>
</tbody>
</table>

II. Associated hereditary and/or familial diseases

Ten (2.8%) of the 355 patients with primary hydrocephalus had siblings with hydrocephalus, seven males, two females, and one unspecified, of whom three patients had simple hydrocephalus and seven had complicated hydrocephalus (3 agenesis of the corpus callosum, 2 myelomeningocele, 1 encephalocele, and 1 Dandy-Walker malformation).

Fifteen (4.2%) of the 355 patients with primary hydrocephalus (10 males and 5 females) had syn-
Table 3  Cases of complicated primary hydrocephalus according to causative and associated central nervous system (CNS) lesions

<table>
<thead>
<tr>
<th>Causative and associated CNS lesions</th>
<th>Fetal hydrocephalus</th>
<th>Infantile hydrocephalus</th>
<th>Unspecified hydrocephalus</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelomeningocele</td>
<td>44</td>
<td>44</td>
<td>3</td>
<td>91</td>
</tr>
<tr>
<td>Chiari 2</td>
<td>29</td>
<td>21</td>
<td>2</td>
<td>52</td>
</tr>
<tr>
<td>Chiari 1</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Agenesis of corpus callosum</td>
<td>23</td>
<td>7</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>Dandy-Walker malformation</td>
<td>14</td>
<td>15</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>Encephalocele</td>
<td>11</td>
<td>9</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Arachnoid cyst</td>
<td>3</td>
<td>8</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Poren-, schizen-, hydranencephaly</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Cerebral dysgenesis</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Syringomyelia</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Occult spinal dysraphism</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Choroid plexus dysraphy</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Achondroplasia</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>16</td>
<td>11</td>
<td>0</td>
<td>27</td>
</tr>
</tbody>
</table>

Discussion

Hydrocephalus is commonly associated with other CNS pathologies, which may adversely affect the prognosis. In our nationwide survey of congenital hydrocephalus, around 90% of cases were classified as primary hydrocephalus and only about 10% as secondary hydrocephalus. The ratio of secondary hydrocephalus in our study is clearly lower than those in other reports, where the etiology of hydrocephalus was intracranial hemorrhage in 10–30% of the cases with congenital hydrocephalus and intracranial infection in 5–20%. This might be related with the low reply rate in patients with intracranial hemorrhage or infection because of the poor prognosis and difficulties in treatment which were suspected in our questionnaire survey. Of the patients with primary hydrocephalus, about 80% had other accompanying CNS anomalies (complicated hydrocephalus). Therefore, the majority of cases of congenital hydrocephalus are complicated hydrocephalus, which present with various problems related to management. Marked predominance of complicated hydrocephalus was observed in both fetal hydrocephalus and infantile hydrocephalus.

The time of diagnosis of hydrocephalus differed significantly between the types of complicated hydrocephalus. The predominance of these complications would be related to the difference in the time of diagnosis of hydrocephalus in each patient, which in turn would be related to etiology. Marked predominance of holoprosencephaly, congenital destructive cystic lesions, and agenesis of the corpus callosum was noted in the fetal hydrocephalus group, possibly because cystic lesions and distinct dysgenetic lesions of the brain are identified more easily by prenatal ultrasonography. However, arachnoid cyst, the most representative intracranial cystic lesion, was predominant in the infantile hydrocephalus group. Myelomeningocele, present in about 30% of the patients in this group, tends to be overlooked by ultrasonography unless the lesion is sufficiently large to visualize, but over half of the cases were identified prenatally, probably because of the association with hydrocephalus.

The fact that arachnoid cyst was exceptionally predominant in the infantile hydrocephalus group suggests a different natural history from other CNS cystic lesions and mainly postnatal development. Analysis of 54 fetuses with prenatally diagnosed intracranial cysts found that 45% of the cysts were detected after the 30th week of gestation, in contrast to normal ultrasonography findings at 22 weeks. Sylvian cysts, which are overwhelmingly dominant in childhood, and hydrocephalus, which is frequently
associated with intracranial cysts in children, were both rare. These findings demonstrate that both intracranial cysts and accompanying hydrocephalus develop late in pregnancy or postnatally. This observation might explain the exceptional predominance of arachnoid cyst in the infantile hydrocephalus group.

Among the causes of secondary hydrocephalus, tumor was predominant in the fetal hydrocephalus group and infection was predominant in the infantile hydrocephalus group. This tendency seems to reflect the fact that tumors are easily detectable by intrauterine ultrasonography and/or MR imaging because of the distinctive features and secondary changes, such as shift or deformity of the ventricles and other surrounding structures. On the other hand, detection of hydrocephalus caused by infectious disease is considered difficult because of the few distinguishing morphological features in prenatal imaging studies.

The role of ultrasonography in recognizing the cause of fetal hydrocephalus was reported by many authors. However, prenatal diagnosis based on an early ultrasound scan is not always reliable as ventriculomegaly usually starts after 20 weeks of gestation, the importance of additional clinical investigations is stressed. There are also many reports which described the importance of MR imaging for correct diagnosis and reliable prognosis, even though incomplete myelination and gyration may lead to difficulty in analysis. As MR imaging can give some idea of the prognosis by evaluating the myelination pattern, which is not possible with ultrasonography, it provide significant additional information that can affect parent counseling, prenatal intervention, and postnatal management. Statistical evaluation of the relationship between age at diagnosis or initial surgery for hydrocephalus and neurodevelopmental outcome suggested that etiology was a major determinant of outcome in children who underwent early postnatal surgical treatment of fetal hydrocephalus. The relationship between the etiology and clinical outcome in the patients identified by the current survey will be reported in a subsequent paper.

About 3.0% of patients with primary hydrocephalus had siblings with hydrocephalus, and many of these patients had various chromosomal aberrations or syndromic congenital anomalies. Almost all cases were infantile hydrocephalus. Anomalies outside the CNS, such as cardiac anomalies and cleft lip, were common in patients whose siblings had hydrocephalus and in patients who had syndromic congenital anomalies. A study on the etiology and presumed recurrent risk of siblings in a series of 35 patients with congenital hydrocephalus in combination with aqueduct stenosis identified a genetic etiology in 13 patients (37.1%) with an increased recurrence risk for siblings. Fifteen of 155 cases of prenatally detected mild ventriculomegaly had associated chromosomal anomalies, all of which occurred in the presence of other major anomalies. Although chromosomal abnormalities are rarely associated with hydrocephalus in general, a karyotype study will be necessary to investigate hereditary or familial factors that might predispose individuals to hydrocephalus. Despite the significant limitations of this retrospective study, the findings provide a guide for preoperative counseling of patients and their families to help them maintain realistic expectations about outcome. The results regarding the etiological distribution of congenital hydrocephalus may provide the basis for the future development of better management and for defining standards.

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Address reprint requests to: Kouzo Moritake, M.D., Department of Neurosurgery, Shimane University School of Medicine, 89-1 Enya-cho, Izumo, Shimane 693–8501, Japan.

**Commentary**

The authors have analyzed a nationwide survey on the etiology and associated conditions of prenatally and postnatally diagnosed congenital hydrocephalus. They received information on 393 patients. The vast majority of patients had primary hydrocephalus. In this group, the majority had associated CNS anomalies including holoprosencephaly, agenesis of the corpus callosum, and cystic lesions. While the results are somewhat typical of previous analyses of the etiology of hydrocephalus, the authors should receive credit for conducting this survey and acquiring the data. As with any survey, it would be nice to know the response rate, the co-operativity of the pediatricians and obstetricians, and the time of the diagnosis in utero or after delivery. Regional rate reporting and sample size errors may be some of the additional limitations to this study. Still, the authors have amassed a sizeable dataset on congenital hydrocephalus in Japan, and this information should be of value when professionals, including neurosurgeons, are asked to counsel families whose fetus or baby is diagnosed with congenital, primary hydrocephalus.

James T. RUTKA, M.D., F.R.C.S.C., F.A.C.S., F.A.A.P.
Dan Family Chair in Neurosurgery
Division of Neurosurgery
The University of Toronto
Toronto, Ontario, Canada

This is a very interesting paper. The authors reported 393 patients with congenital hydrocephalus. 193 patients suffered from fetal hydrocephalus and 181 patients had infantile hydrocephalus. The majority of cases of congenital hydrocephalus were primary hydrocephalus. Destructive cystic lesion, holoprosencephaly, and agenesis of the corpus callosum were predominant in fetal hydrocephalus. Arachnoid cyst was common seen in infantile hydrocephalus.

Hydrocephalus unassociated with neural tube defect is a clinical entity of diverse etiology. There is an excess of males affected with hydrocephalus, resulting from the existence of a well-defined X-linked recessive form of the condition. It was suggested that in some cases of congenital hydrocephalus the etiology was the same as that of neural tube defects. Consideration should therefore be given to possible primary prevention and to the need for appropriate antenatal investigation to detect and deal with congenital hydrocephalus.

Evaluation of fetal central nervous system (CNS) by ultrasonography is frequently limited, particularly in the early stage of gestation and ultrasonography findings are occasionally inconclusive or are insufficient for prenatal diagnosis or for guiding treatment choices. Fetuses with questionable abnormal ultrasonography findings should be sent for further evaluation with MRI. The later is helpful to detect fetal CNS abnormalities, and it is a supplement to ultrasonography in complicated pregnancies.

**References**

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Shuyuan YANG, M.D.
Department of Neurosurgery
Tianjin Medical University Hospital
Tianjin, P.R.C.