A clinical and neuroradiological study of X-linked hydrocephalus in Japan

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To clarify the clinicopathological features of X-linked hydrocephalus, the authors studied 30 affected males from 15 families. In utero ultrasonography, performed at 21 to 40 weeks of gestation, revealed 18 fetuses with hydrocephalus. Computerized tomography (CT) revealed bilateral enlargement of the lateral ventricle with preponderant dilation of the posterior horn. In five patients with complete magnetic resonance (MR) imaging data, the most specific finding was localized atrophy of the anterior vermian lobe. Other MR imaging findings included a large massa intermedia, flat corpora quadrigemina, a small brainstem, and diffuse hypoplasia of the cerebellar white matter. In all cases, the corpus callosum was hypoplastic or aplastic. The aqueduct was patent in four of five cases. Asymmetrical reduction of the ventricular size and a rippled ventricular wall were characteristic postshunt CT findings. Progressive macrocephaly and symptoms due to increased intracranial pressure were ameliorated by the shunt; however, the neurological outcome was not improved by shunting. Of 14 patients who lived to be between 2 and 18 years of age, all are retarded. These results indicate that X-linked hydrocephalus is not a disease of simple ventriculomegaly due to aqueduct stenosis alone but involves other complicated central nervous system anomalies.

KEY WORDS • X-linked hydrocephalus • chromosome • fused thalamus • vermis • ventriculoperitoneal shunt
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**Results**

Twenty-three patients from 10 families were classified as definite cases and seven patients from five families as probable cases (Table 1). Figure 1 shows representative pedigrees of Families D and H.

**Time and Method of Diagnosis**

Of the 23 definite cases, 14 (61%) were diagnosed in utero between 21 and 40 weeks of gestation (mean 33.6 weeks), seven patients (30%) at birth (Day 1), and the remaining two (9%) at 19 days and 2 months of age. Of seven probable cases, four (57%) were diagnosed in utero between 24 and 38 weeks of gestation (mean 32.5 weeks), and three (43%) at birth. In all 18 patients diagnosed in utero, hydrocephalus was demonstrated by ultrasonography. Of the 12 patients diagnosed after birth, hydrocephalus was demonstrated by CT in seven and by pneumoencephalography in one.

**Imaging Studies**

Preshunt CT scans were evaluated in 12 cases (Fig. 2) and all of them showed marked bilateral enlargement of the lateral ventricle. The posterior horn of the lateral ventricle was preponderantly enlarged in five cases. The size of the third ventricle differed from case to case, and there was no enlargement of the fourth ventricle. There was no conspicuous brain atrophy, but the cortical mantle was thin. Postshunt CT images were evaluated in eight patients. Of six patients in whom the ventricular tip of the shunt was in the lateral ventricle, four manifested asymmetrical reduction of the shunted ventricle. In all patients the wall of the lateral ventricle was rippled rather than smooth (Fig. 3).

Magnetic resonance images obtained after shunt placement were studied in six patients aged from 1 to 12 years (Fig. 4 and Table 2). The aqueduct of Sylvius was patent in four patients, not patent in one, and could not be evaluated in the other. The corpus callosum was hypoplastic in five patients and aplastic in one. The massa intermedia was enlarged in all six patients. The quadrigeminal plate was flat in five patients and the brainstem was small in all six cases. Localized atrophy of the anterior vermis (lingu-
la, central lobule and culmen,\textsuperscript{12} or lobules I to V\textsuperscript{15}) was noted in all five patients whose midsagittal MR images were available. The folia in these lobules were shrunken and the precentral cerebellar and primary fissures were widened; however, the white matter branching from the corpus medullare into these lobules was no thinner than in the other vermician lobules. The other portions of the vermis and cerebellar hemisphere were not atrophic. The cerebral white matter was diffusely thin in all six patients. The dura mater in the cerebral convexity and falx was thickened in three cases.

Ventriculograms were studied in three patients after the shunt operation. The results were variable. In one patient, who underwent ventriculography upon malfunction of his ventriculoperitoneal shunt, no occlusion of the cerebrospinal fluid (CSF) flow was disclosed (Fig. 5). In another patient, the contrast medium remained in the injected lateral ventricle, suggesting occlusion of the foramen of Monro. In the third patient, the contrast medium filled both the lateral and third ventricles, indicating occlusion of the aqueduct.

Adduction-Flexion Deformity of the Thumb

Adduction-flexion deformity of the thumb was present in 23 (77\%) of the 30 patients. It was present in 20 (87\%)}

**TABLE 2**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Case 7</th>
<th>Case 11</th>
<th>Case 12</th>
<th>Case 15</th>
<th>Case 17</th>
<th>Case 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>age at study (yrs)</td>
<td>12</td>
<td>4</td>
<td>4</td>
<td>1.6</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>atrophy of anterior vermis</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>enlarged massa intermedia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>flat quadri</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>germinal plate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aqueduct patent</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>hypoplasia (H) or aplasia (A) of corpus callosum</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>A</td>
<td>H</td>
</tr>
<tr>
<td>hypoplasia of white matter</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>thickened dura mater</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

* M = midsagittal image suboptimal for analysis because of motion artifact. + = factor present, − = factor absent.
of the 23 patients in the definite group, and in three (43%) of the seven patients in the probable group (Fig. 6).

Treatment and Outcome

Of the 23 patients in the definite group, 14 received ventriculoperitoneal and two ventriculoatrial shunts. Of the seven patients in the probable group, four underwent ventriculoperitoneal shunting. Of 10 patients who received no treatment, only one survived and he is severely retarded. His head circumference was 89 cm at the age of 3 years. Of the 20 patients who underwent a shunt operation, 14 are alive and between 2 and 18 years of age, five died (at 6 days to 3 years old), and one was lost to follow-up review. Of the survivors, 11 are severely retarded (need total care, not locomotive, intelligence quotient (IQ) less than 50), and three are moderately retarded (need assistance, walk or creep with support, IQ between 50 and 70).

Postmortem Pathological Findings

Four patients (Cases 5, 19, 20, and 21) were examined at autopsy.\(^{18,19}\) The brain weighed 320 g in Case 5 and 135 g in Case 21. On axial section, the lateral ventricle was markedly dilated in Cases 5, 19, and 21 and moderately dilated in Case 20. The aqueduct was patent in all four cases; in two patients it was narrow and in one of them subependymal rosette formation was found. The corpus callosum was hypoplastic or aplastic in all cases. Hypoplasia or absence of the pyramidal tract in the medulla was identified in two cases. One patient had a fused thalamus.

Discussion

The overall incidence of fetal hydrocephalus has been reported by Hudgins, et al.,\(^{11}\) to be 0.5 to 2 per 1000 total births. They stated that only one-fourth of these were live births and one-half of those born alive showed normal intellectual development. In X-linked hydrocephalus, the neurological outcome is very poor. Thus, diagnostic methods for fetal hydrocephalus, especially X-linked hydrocephalus, early in pregnancy would be very useful. Willems and colleagues\(^{20}\) localized a gene for X-linked hydrocephalus to Xq28 by linkage analysis. Rosenthal, et al.;\(^{22}\) found a point mutation of the gene for neural cell
adhesion molecule L1 that maps to the locus of Qx28. At present, there is no genetic diagnosis of X-linked hydrocephalus, and it is impossible to detect female carriers because they are asymptomatic.

Fetal ultrasonography has been reported to be useful for the early diagnosis of hydrocephalus. Van Egmond-Linden, et al., and Kelley, et al., reported an abnormal increase in the lateral ventricular width/hemispheric width ratio at 18 or 19 weeks of gestation in cases at risk for X-linked hydrocephalus. In our series, the earliest detection of ventriculomegaly by ultrasonography was made at 21 weeks of gestation. Brocard, et al., recommended sequential sonographic monitoring every 2 to 4 weeks starting at 16 weeks for pregnant women with a carrier status. However, prenatal sonographic diagnosis of affected males is thought not to be fully reliable because the onset of hydrocephalus is variable.

On CT, patients with X-linked hydrocephalus demonstrated symmetrical dilation of the lateral ventricle. Disproportionate enlargement of the posterior horn was frequently observed. The size of the third ventricle varied, and the fourth ventricle was not enlarged. In our series, we failed to detect any pathognomonic features of X-linked hydrocephalus on CT before treatment. However, post-shunt CT revealed unique features, namely an asymmetrical reduction in the size of the shunted lateral ventricle as well as the presence of a rippled ventricular wall. We doubt that these findings are attributable to excessive CSF drainage or problems related to surgery, because CT images obtained at different institutions where different shunt systems were used had these features in common. We therefore posit that abnormalities in the ependyma or the subependymal structure, which is vulnerable to changes in intraventricular pressure, play a role.

To our knowledge, no MR imaging studies of X-linked hydrocephalus have been reported. The number of patients in whom MR images were obtained is small; in our series, six patients were studied by MR imaging after shunt placement. Despite this, we suggest that our MR imaging findings further the understanding of the pathophysiology of X-linked hydrocephalus. For example, localized atrophy of the anterior vermian lobules is a conspicuous and specific finding in X-linked hydrocephalus. Courchesne, et al., showed that the precuneate, prepyramidal, and primary fissures are relatively wide and easily discernible on MR images of normal subjects. In five of our six patients, the precentral cerebellar and primary fissures were markedly widened. The folia were thin and the sulci were wide and deep. Hypoplasia or agenesis of the vermis has been reported for various other pathological states. In patients with such partial atrophy of the vermis, the anterosuperior lobules were found to be preserved. This can be explained by the fact that, during fetal development, the vermis fuses from the rostral to the caudal end. The other portion of the vermis and the cerebellar hemisphere were not atrophic in our patients. The anterior vermian lobe consists of three lobules (lingula, central lobule, and culmen), as designated by Ito. These correspond to lobules I to V in the nomenclature of Larsell. These lobules phylogenetically belong to the paleocerebellum, which also includes the pyramids and uvula of the posterior vermian lobe. The paleocerebellum contains fibers of the spinocerebellar and cuneocerebellar tracts, which transmit the input from deep sensations, chiefly from the muscle spindle. The paleocerebellum has little cerebral cortical input. It sends efferent fibers to the red nucleus, which connects with the caudate nucleus, putamen, and spinal motor neurons. According to our MR imaging results, atrophy was localized to the cortex of the anterior vermian lobe; the pyramids and uvula were not atrophic. Detailed neuropathological studies may shed light on the possible relationship between pathophysiology and localized atrophy of the anterior vermian lobe in X-linked hydrocephalus.

Other MR imaging findings common to all of our patients were a large massa intermedia, flat corpora quadrigemina, and diffuse hypoplasia of the cerebral white matter. In X-linked hydrocephalus, various ocular symptoms like nystagmus, strabismus, roving eye movement, setting sun phenomenon, and ptosis were reported to occur. An anomaly of the quadrigeminal plate may be related to some of these ocular findings. A large massa intermedia (referred to as “fusion of the thalamus” or “fused thalamus” in the literature) is frequently present in patients with holoprosencephaly or a Chiari II malformation. Sato hypothesized that a fused thalamus resulted in narrowing of the third ventricle, even in patients who have dilated lateral ventricles due to Chiari II malformation. A similar feature was observed in the case of X-linked hydrocephalus. In addition, two of our four patients who came to autopsy exhibited hypoplasia of the pyramid in the medulla, a finding that has also been reported by Halliday, et al. In our MR imaging studies, the brainstem was slender on sagittal images; however, we could not conclude from these studies alone that this was due to the absence of the pyramid. Based on their detailed autopsy study, Chow, et al., proposed that congenital bilateral absence of the pyramids is strongly associated with X-linked hydrocephalus.

There is a controversy as to whether aqueductal stenosis is the primary cause of hydrocephalus. In the early literature, aqueductal stenosis or a focal heaping-up of ependymal cells in the preaqueductal tissue, the presence of rosettes, or forking were proposed as the primary mechanisms of ventricular dilation. In 1979, however, Landrieu, et al., reported a patient with X-linked hydrocephalus who manifested no stenosis of the aqueduct. They argued that the reduction of the aqueductal caliber was produced secondarily by lateral compression of the lateral and third ventricles. Their hypothesis was strengthened by similar findings reported by others. Renier, et al., proposed a new terminology for this disease, “X-linked congenital hydrocephalus,” instead of “X-linked aqueductal stenosis.” In our series, MR images demonstrated patency of the aqueduct in four of five patients with adequate imaging studies available. The ventriculogram showed no occlusion of CSF flow in at least one of three patients and the aqueduct was found to be patent in all four patients with autopsy. Thus, we conclude that aqueductal stenosis is not the primary cause of X-linked hydrocephalus.

The neurological outcome has been reported to be very poor in X-linked hydrocephalus. In our series, even though shunts were placed in early infancy, shunt proce-
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dures did not improve the patients’ neurological condition except for preventing progressive macrocephaly. We consider this to be further evidence that the primary pathophysiology of X-linked hydrocephalus is not ventricular dilation due to aqueductal stenosis. Besides the morphological abnormalities that are detected by MR imaging or autopsy examination, microscopic studies have revealed cortical malformation and poor differentiation and maturation of cortical neurons.7,10,22 Recent molecular genetic studies implicate an abnormal neural cell adhesion molecule, L1, in the genesis of X-linked hydrocephalus.4,22

In 1974, Bianchine and Lewis1 reported a syndrome (“MASA”) comprised of mental retardation, aphasia (late speech development), spastic paraplegia, and adducted thumbs.2 The clasped thumb without hydrocephalus may exist as an isolated hereditary X-linked form.2,8 This malformation has been reported in 25% to 50% of patients6 with X-linked hydrocephalus, and was present in 77% of our patients. The phenomenon of X-linked hydrocephalus, the MASA syndrome,4,8 and isolated clasped thumbs may be variable expressions of the disease caused by the same genetic abnormality. Molecular genetic analysis will not only answer this question but may also facilitate the development of prenatal diagnostic methods to test affected males and asymptomatic female carriers.

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References


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