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主論文

X-linked hydrocephalus in Japan

- Clinical and neuroradiological study -

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Abstract

To clarify the clinicopathological features of X-linked hydrocephalus, we studied 30 affected males from 15 afflicted families. In utero ultrasonography, performed between 21 and 40 weeks of gestation, showed 18 fetuses with hydrocephalus. CT exhibited bilateral enlargement of the lateral ventricle with preponderant dilatation of the posterior horn. In all 5 patients studied, the most specific MRI finding was localized atrophy of the anterior vermian lobe. Other MRI findings included large massa intermedia, flat corpora quadrigemina, small brain stem and diffuse hypoplasia of the cerebral white matter. In all cases, the corpus callosum was hypoplastic or aplastic. The aqueduct was patent in 4 of 5 cases. Asymmetrical reduction of the ventricular size and a wavy ventricular wall were characteristic post-shunt CT findings. Progressive macrocephaly and symptoms due to increased intracranial pressure were ameliorated by the shunt. On the other hand, the neurological outcome was not improved by the shunt: of 14 patients who lived to be between 2 and 18 years, all are retarded. Our results indicate that X-linked hydrocephalus is not a disease of simple ventriculomegaly due to aqueduct stenosis alone but a disease involving other complicated central nervous system anomalies.

Introduction

X-linked hydrocephalus (Mckusick No. 307000)[17] is one of the genetic forms of hydrocephalus. This hydrocephalus was first described by Bickers and Adams in 1949.[2] Edwards reported 4 families with 29 afflicted individuals in 1961.[7] Since then, it has been called Bickers-Adams-Edwards syndrome. Originally, this syndrome was thought to be characterized by hydrocephalus, stenosis of the aqueduct, adducted thumbs, and spastic paraparesis.[7] However, since Landrieu et al.[14] reported a case without aqueductal stenosis in 1979, there has been increasing evidence that the reduction of the caliber of the aqueduct may be produced secondarily by compression of the dilated ventricle.

Neuropathologically there are other morphological anomalies, for example aplasia of the corpus callosum[27] and pyramid in the medulla[9] besides ventriculomegaly. However, these anomalies are also seen in patients with Chiari II malformation[24] and are not specific to X-linked hydrocephalus. The literature contains few CT studies of afflicted individuals and to our knowledge, no MR studies have been published. Reliable neuroradiological criteria specific to X-linked hydrocephalus would be useful, especially for the diagnosis of non-familial, sporadic cases to differentiate them from hydrocephalus due to other causes, and for genetic counseling. We collaborated with members of the Japanese Society for Pediatric Neurosurgeons associated with Children's Hospital (JSPNCH), and report the clinical and neuroradiological features of this syndrome in Japan.

Clinical materials and methods

We reviewed clinical data of 30 affected males from 15 families with X-linked hydrocephalus. Of these, 14 patients from 6 families were treated by us, data on 10 patients from 6 families were provided by members of JSPNCH, and data on 6 patients from 3 families were obtained from reports published by Japanese authors.[16,19,20]

We classified the patients as definitive or probable X-linked hydrocephalus based on clinical features and family history as described by Halliday et al.[9] We classified the patient as a definitive case, (1) if males of more than one generation, related through females were affected or (2) if two brothers with hydrocephalus exhibited the typical thumb lesions. We classified the patient as a probable case, (1) if two brothers with hydrocephalus did not exhibit the typical thumb lesions, or (2)

if a male patient manifested hydrocephalus and flexed–adducted thumbs without having affected relatives.

Motor and mental development was assessed according to the criteria, based on the severity of cerebral palsy, described by Russman.[23]

Results

There were 23 patients from 10 families who were classified as definitive cases; 7 patients from 5 families were classified as probable cases (Table 1). Figures 1 (a) and (b) show representative pedigrees of families D and H.

Time and method of diagnosis

Of the 23 definitive cases, 14 (61%) were diagnosed in utero between 21 and 40 weeks of gestation (mean 33.6 weeks). Seven patients (30%) were diagnosed at birth (day 1), and the remaining 2 (9%) were diagnosed at 19 days and 2 months of age. Of 7 probable cases, 4 patients (57%) were diagnosed in utero between 24 and 38 weeks of gestation (mean 32.5 weeks), and 3 patients (43%) were diagnosed at birth. In all 18 patients diagnosed in utero, hydrocephalus was demonstrated by ultrasound sonography. In 7 of the 12 patients diagnosed after birth, CT scan revealed hydrocephalus and in one patient, it was demonstrated by pneumoencephalography.

Imaging studies

Preshunt CT images were evaluated in 12 cases (Fig. 2) and all of them, marked bilateral enlargement of the lateral ventricle was observed. The posterior horn of the lateral ventricle was preponderantly enlarged in 5 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 8 patients. Of 6 patients in whom the ventricular tip of the shunt was in the lateral ventricle, 4 manifested asymmetrical reduction of the shunted ventricle. In all patients the wall of the lateral ventricle was wavy rather than smooth (Fig. 3).

MR images after the shunt operation were studied in 6 patients aged from 1 to 12 years (Figs. 4

and 5, and Table 2). The aqueduct of Sylvius was patent in 4 patients, not patent in one, and not available for evaluation in the other one. The corpus callosum was hypoplastic in 5 patients and aplastic in one. The massa intermedia was enlarged in all 6 patients. The quadrigeminal plate was flat in 5 patients and the brain stem was small in all 6 cases. Localized atrophy of the anterior vermis (lingula, centralis and culmen[12], or lobules I to V[15]) was noted in all 5 cases whose midsagittal images were available. In these lobules, the folia were shrunken. The precentral cerebellar and primary fissures were widened. However the white matter branching from the corpus medullare into these lobules was not thinner than in the other vermian lobules. The other portion of the vermis and cerebellar hemisphere were not atrophic. The cerebral white matter was diffusely thin in all 6 patients. The dura mater in the cerebral convexity and falx was thickened in 3 cases.

Ventriculograms were studied in 3 patients after the shunt operation. The results were variable. However, in one patient who underwent ventriculography upon demonstrating malfunction of the ventriculo-peritoneal shunt, no occlusion of the cerebrospinal fluid (CSF) flow was disclosed (Fig. 6). In the other patient, the contrast medium stayed in the injected lateral ventricle, suggesting occlusion of the foramen of Monro. In the remaining 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%) of the 23 patients in the definitive group, and in 3 (43%) of the 7 patients in the probable group (Fig. 7).

Treatment and outcome

Of the 23 definitive patients, 14 received a ventriculo-peritoneal and 2 a ventriculo-atrial shunts. Of the 7 probable patients, 4 underwent ventriculo-peritoneal shunts. Ten patients received no treatment, only one survived and 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, 5 died (6 days to 3 years old) and one was lost from follow-up. Of the survivors, 11 are severely retarded (need total care, not locomotive, IQ less than 50), and 3 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 autopsied.[18,19] The brains weighed 320 g in cases 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 4 cases. In 2 patients it was narrow and in one of the 2 patient 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 to be 0.5 to 2 per 1,000 total births.[11] Hudgins et al. reported that only one fourth of these were live births and half of the live births showed normal intellectual development.[11] In X-linked hydrocephalus, the neurological outcome is very poor. Thus, diagnosing methods for fetal hydrocephalus, especially X-linked hydrocephalus, early in pregnancy would be very useful. Willems et al.[30,31] 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 which maps to the locus of Xq28. At present, there is no genetic diagnosis of X-linked hydrocephalus. 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.[25] and Kelley et al.[13] reported an abnormal increase in the LV/HW (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 ultrasound sonography was made at 21 weeks of gestation. Brocard et al.[3] recommended sequential sonographic monitoring every 2 to 4 weeks starting at 16 weeks for pregnant woman in the 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, X-linked hydrocephalus demonstrated symmetrical dilatation 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 X-linked hydrocephalus. 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 wavy ventricular wall. We doubt that these findings are attributable to excessive CSF drainage or problems related 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 MRI studies of X-linked hydrocephalus have been reported. The number of patients in whom MRI was studied is small and all MRI was performed after shunt placement in our series. Despite this, we suggest that our MRI findings further the understanding of the patho-physiology 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.[6] showed that the preculminate, prepyramidal and primary fissures are relatively wide and easily discernible on MRI of normal subjects. In our series, 6 patients were studied by MRI after shunt placement. In 5 patients, the precentral cerebellar and primary fissures were markedly widened. The folia was 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.[15] 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, lobulus centralis and culmen, as designated by Ito.[12] These correspond to lobules I to V in the nomenclature of Larsell.[15] These lobules phylogenetically belong to the paleocerebellum which also includes the pyramis 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.[12] According to our MRI results, atrophy was localized to the cortex of the anterior vermian lobe; the pyramis 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 MRI 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.[21] An anomaly of the quadrigeminal plate may be related to some of these ocular findings. A large massa intermedia (fusion of the thalamus or fused thalamus in the literature) is frequently present in patients with holoprosencephaly or Chiari type II malformation.[24] Sato hypothesized that a fused thalamus resulted in narrowing of the third ventricle, even in patients who have dilated lateral ventricles due to Chiari type II malformation.[24] A similar feature was observed in the case of X-linked hydrocephalus. In addition, 2 of our 4 autopsied patients exhibited hypoplasia of the pyramid in the medulla, a finding that has also been reported in the literature.[9] In our MRI studies, the brainstem was slender on sagittal images, however, we could not conclude based on MRI studies alone, that this was due to the absence of the pyramid. Based on their detailed autopsy study, Chow et al.[5] 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, aqueduct 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 dilatation.[7] In 1979, however, Landrieu et al.[14] 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.[21,25,26,29] Renier et al.[21] 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 4 of 5 patients studied. The ventriculogram showed no occlusion of CSF flow in at least one of 3 patients and the aqueduct

was patent in all 4 autopsied patients. Thus, we conclude that aqueduct 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, shunt procedures did not improve neurological states except for preventing progressive macrocephaly, even though shunts were placed in early infancy. We consider this further evidence that the primary pathophysiology of X-linked hydrocephalus is not ventricular dilatation due to aqueduct stenosis. Besides the morphological abnormalities that are detected by MRI or autopsy studies, microscopic studies have revealed cortical malformation, and poor differentiation and maturation of cortical neurons.[7,10,27] 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 Lewis[1] 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.[28] This malformation has been reported to be present in 25 to 50% of patients[9] with X-linked hydrocephalus, it was present in 77% of our patients. X-linked hydrocephalus, MASA syndrome[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.

Figure legends

Figure 1

Pedigrees of families D(a) and H(b). The pedigree pattern is consistent with an X-linked recessive inheritance.

Figure 2

CT scans of case 18 on day 1 of life demonstrating marked dilatation of the lateral ventricle. Note preponderant enlargement of the posterior horn and the small fourth ventricle. The third ventricle was enlarged.

Figure 3

CT scan of case 11 after ventriculo-peritoneal shunt demonstrating asymmetrical reduction of the shunted lateral ventricle and a wavy ventricular wall.

Figure 4

MR images of case 17 at the age of 9 years. The patient had a ventriculo-peritoneal shunt.
(a) T1 weighted sagittal image demonstrating flat corpora quadrigemina, atrophy of the anterior vermian lobule and hypoplasia of the corpus callosum.
(b) T2 weighted sagittal image demonstrating a patent aqueduct of Sylvius.
(c) T1 weighted coronal image demonstrating a fused thalamus and thickened falx. The third ventricle was compressed upwards by the deformed thalamus.

Figure 5

MR images of case 12 at the age of 4 years. The patient underwent a ventriculo-peritoneal shunt.
(a) T1 weighted axial image demonstrating diffuse hypoplasia of the cerebral white matter.
(b) T1 weighted sagittal image demonstrating flat corpora quadrigemina, atrophy of the anterior vermian lobule and hypoplasia of the corpus callosum.
(c) Magnified view of the posterior fossa in Fig. 4 (b) demonstrating atrophy of the anterior vermian lobule.

Figure 6

Ventriculogram (left) and schematic illustration (right) of case 7 who manifested malfunction of the shunt. Note that the contrast medium filled the dilated third ventricle, and flowed out through the patent aqueduct to the fourth ventricle.

Figure 7

Adduction-flexion deformity of the thumb in case 18.

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Summary of the cases

Case		Reporter	Family	Year of birth	Diagnosis Age & Method		Adducted thumbs	Treatment	Outcome	Others
I	1	Odo	A	1973	day19	PEG	+	VA	unknown	
	2			1969	day1		+	*	alive s.	
	3	Matuda	B	1978	3Mo	CT	−	VP	alive m.	
	4			1982	(39wk)	US	+	VA	alive m.	Hirschsprung dis.
	5	Mochizuki	C	1979	(38wk)	US	+	VP	died 〈day 6〉	aut.
	6			1975	day1		+	*	died 〈day 1〉	
	7	Fujitani	D	1985	(40wk)	US	+	VP	alive s.	MRI VG
	8			1979	day1	CT	+	VP	alive s.	
	9	Fujiwara & Tsuchida	E	1983	(38wk)	US	+	VP	died 〈3years〉	
	10			1986	(38wk)	US	+	VP	died 〈10Mo〉	
	11	Sato	F	1986	day1	CT	+	VP	alive s.	MRI VG
	12			1988	(32wk)	US	+	VP	alive s.	MRI
	13	Kobayashi	G	1986	(36wk)	US	+	VP	died 〈12Mo〉	
	14			1991	(39wk)	US	+	VP	alive s.	
	15	Morimoto	H	1992	(29wk)	US	+	VP	alive s.	MRI VG
	16			1965	day1		+	*	died 〈day 1〉	
	17	Yamasaki	I	1982	day1	CT	+	VP	alive m.	MRI
	18			1987	(37wk)	US	+	VP	died 〈10Mo〉	
	19			1987	(27wk)	US	+	*	fetal death	aut.
	20			1987	(23wk)	US	−	*	aborted	aut.
	21			1989	(21wk)	US	−	*	aborted	aut.
	22	Aoki	J	1986	day1		+	*	died	
	23			1988	(34wk)	US	+	VP	alive s.	
II	24	Oi	K	1987	(38wk)	US	−	*	died 〈3Mo〉	
	25			1989	(30wk)	US	−	*	fetal death	
	26	Tsuchida	L	1980	day1	CT	+	VP	alive s.	
	27	Fujitani	M	1988	(38wk)	US	+	VP	alive s.	
	28	Morimoto	N	1989	(24wk)	US	−	VP	alive s.	MRI
	29			1984	day1	CT	−	*	died	
	30	Yamasaki	O	1975	day1	CT	+	VP	alive s.	

I = definite X-linked cases.
II = probable X-linked cases.
( ) = gestation at time of prenatal diagnosis.
US = ultrasound sonography
Mo = month
wk = week
PEG = pneumoencephalography
+ = present
− = absent
VP = ventricular-peritoneal shunt
VA = ventricular-atrial shunt
* = untreated
s. = severely retarded
m. = moderately retarded
〈〉 = time of death
aut.= autopsied
VG = ventriculography

TABLE 2

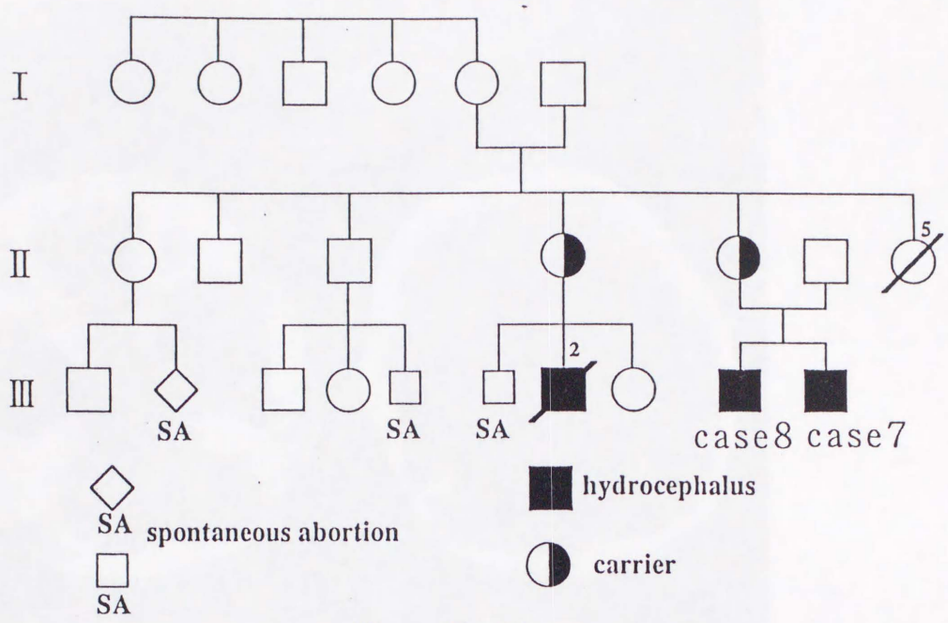
Summary of MRI findings

	case7	case11	case12	case15	case17	case28
Age at study	12 years	4 years	4 years	1.6 year	11 years	3 years
Atrophy of anterior vermian lobule	*	+	+	+	+	+
Enlarged massa intermedia	+	+	+	+	+	+
Flat Co. quadrigemina	+	+	+	+	+	–
Aqueduct	*	p	p	no pat.	p	p
Hypoplasia or Aplasia of corpus callosum	hypo	hypo	hypo	hypo	a	hypo
Hypoplasia of white matter	+	+	+	+	+	+
Thickened dura mater of convexity and falx	+	–	–	+	+	–

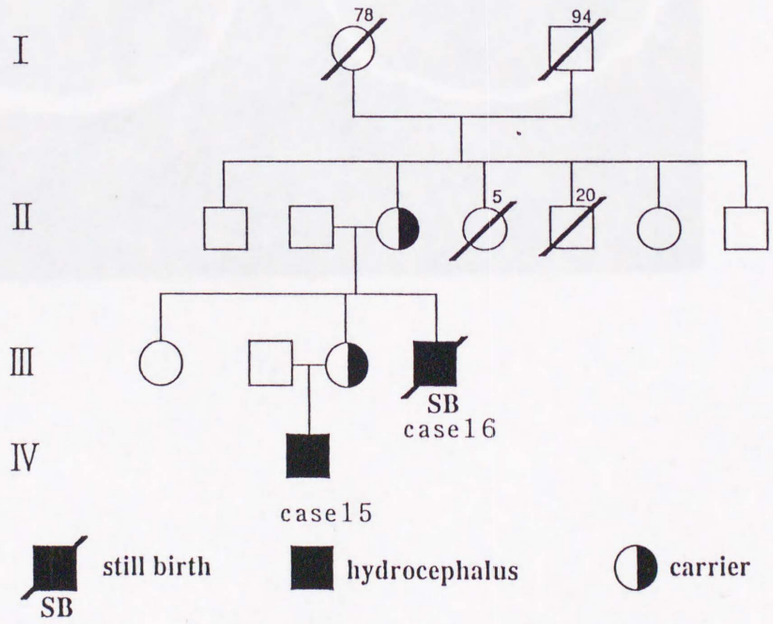
hypo : hypoplasia, a : aplasia, p : patent, no pat.: not patent

* = Midsagittal image suboptimal for analysis,because of mortion artifact.

+ = present, – =absent,



Family D



Family H

Fig 1.

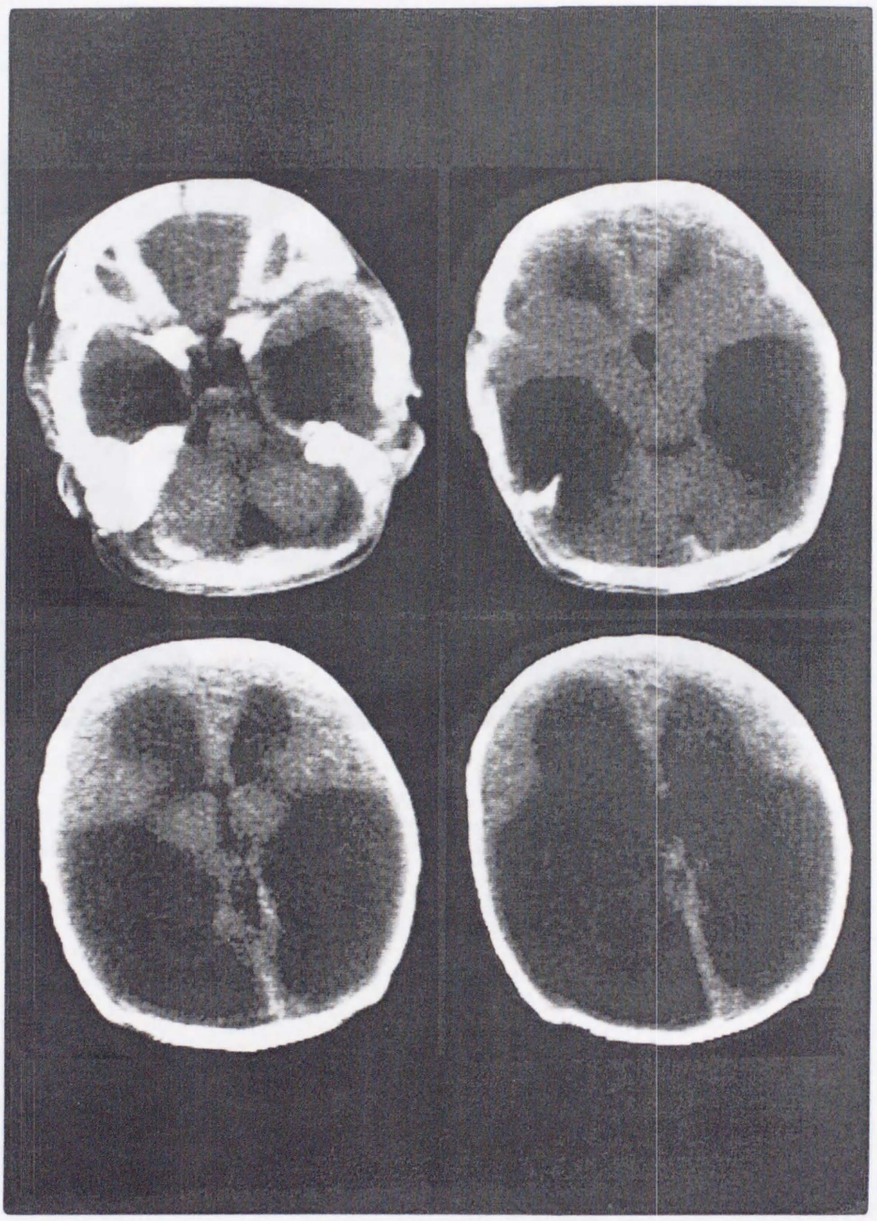


Fig 2.

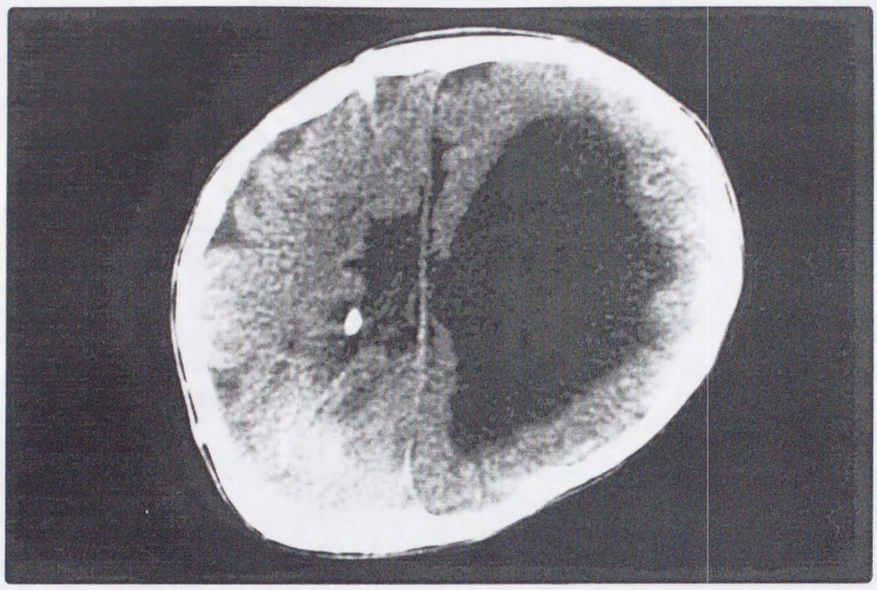


Fig 3

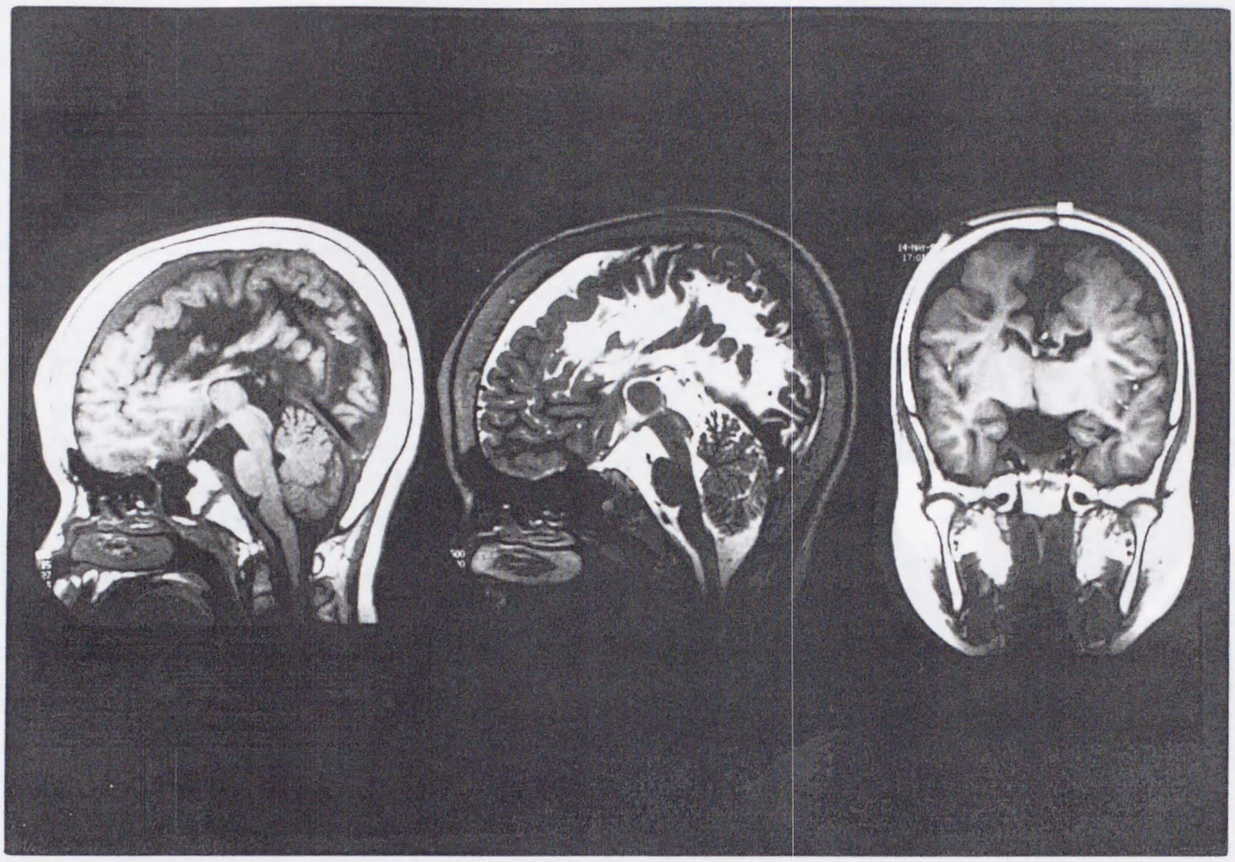


Fig 4

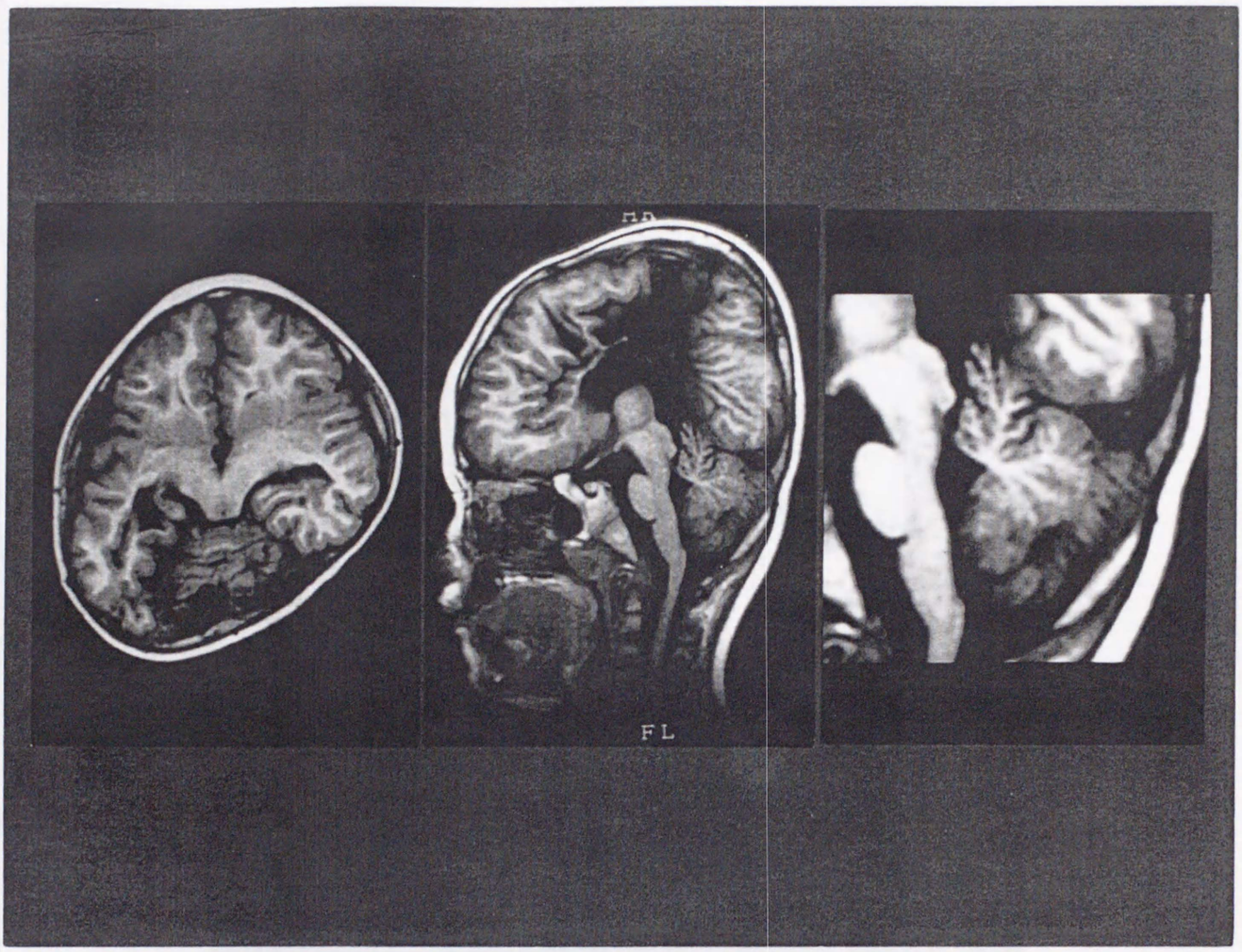
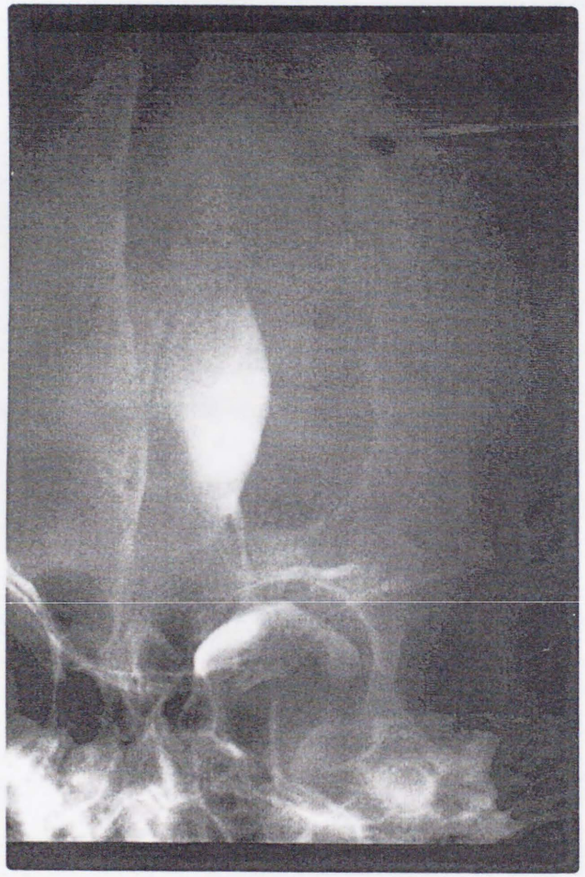


Fig 5



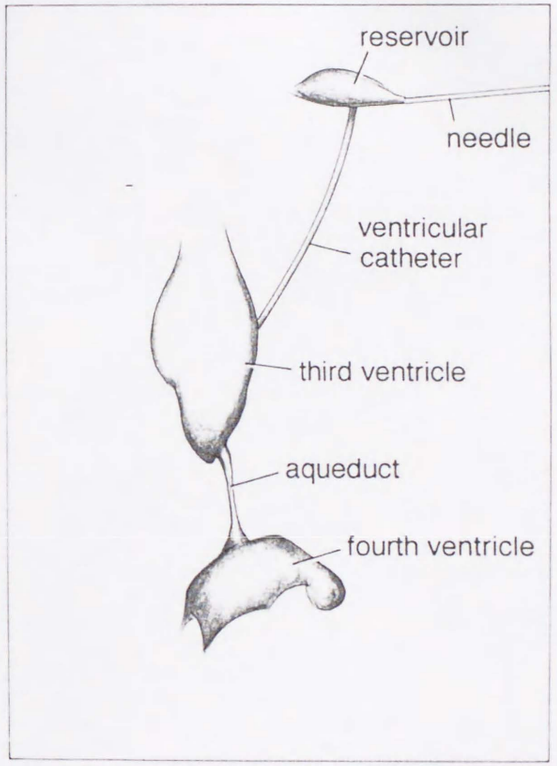

reservoir
needle
ventricular
catheter
third ventricle
aqueduct
fourth ventricle

Fig 6

Fig 7