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Isolated mild fetal cerebral ventriculomegaly: a retrospective analysis of 26 cases

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We retrospectively studied 26 fetuses with isolated mild cerebral ventriculomegaly diagnosed between 1992 and 1998 and defined by a lateral ventricular atrial diameter of 10–15 mm without any other cerebral anomaly. Our objectives were to determine maternal risk factors, to evaluate complementary investigations, to assess developmental prognosis and to propose possible management. During pregnancy 10/26 patients had regressive ventriculomegalies, ten remained borderline at birth and six were confirmed postnatally. No maternal risk factors were identified. Prenatal investigations were carried out in 69% of cases but in only a few cases supplied any information. Postnatal examinations revealed one case of Down syndrome and one of porencephaly. Four children were lost to follow-up. In the 22 other cases, four had developmental delay. Early and unexplained mild ventriculomegaly appears to have a good prognosis. If ventriculomegaly is persistent, prenatal management should be carried out to investigate chromosomal abnormalities, viral infection, and fetal cerebral parenchymal damage. A long postnatal clinical follow-up is required.

KEY WORDS: lateral ventricular diameter; ventriculomegaly; prenatal diagnosis; follow-up

INTRODUCTION

Fetal cerebral ventriculomegaly is a ventricular dilatation which can either be a sign of parenchymal loss (Clewell *et al*., 1985) or of abnormal cerebrospinal fluid circulation. Isolated mild fetal ventriculomegaly can either be stable or slightly progressive, and the developmental prognosis for children seems to be better than currently described for ventriculomegaly associated with abnormal cerebral parenchyma (Valat *et al*., 1998). The risk of developmental delay still remains unclear and partly explains the difficulty in managing these pregnancies. Therefore, we carried out a retrospective study of isolated and mild ventriculomegaly in order to assess prognosis.

PATIENTS AND METHODS

Computer tomography (CT) scan was routinely carried out at 12, 22 and 32 weeks for each patient, who was referred either by their obstetrician or radiologist for suspected ventriculomegaly. Ventriculomegaly was detected on an axial ultrasonographic section at the level of the third ventricle with a measurement of the lateral ventricular atrium as defined by Cardoza *et al.* (1988) (Figure 1). Posterior fossa and median structures were also analysed on appropriate sections. Ultrasonography follow-up examination was routinely performed to confirm the dilatation. At the time of the 22-week scan, biometry and morphology of the fetus were evaluated. Morphologic study included cerebral parenchyma, cerebral ventricular characteristics, corpus callosum, cerebellum, heart cavities, lungs, diaphragm, stomach, kidneys, bladder and limbs.

Cases of isolated mild ventriculomegaly with a ventricular atrial diameter of 10–15 mm at the time of the initial diagnosis were included in the study. However, cases with cerebral or extracerebral malformations (corpus callosum agenesis, porencephaly, Dandy Walker

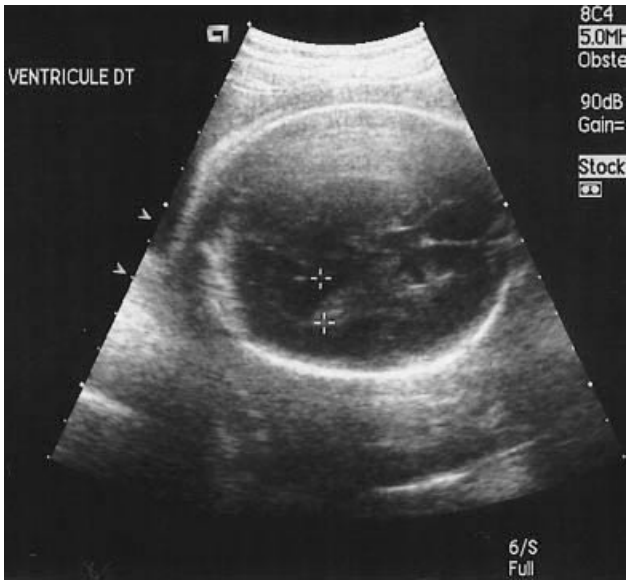

Figure 1—Fetal cerebral ultrasonography carried out at 26 SA (axial tomography). The figure shows unilateral right ventriculomegaly. The right ventricular atrium was measured at 11 mm. The left ventricular was the most superficial and the atrium was measured at 9 mm

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syndrome, holoprosencephaly, myelomengocele, renal hydronephrosis), cerebral calcifications or abnormal-antenatal karyotyping at the time of initial scan were excluded. Cases of ventriculomegaly without indicated measurements and cases with tri- or quadri-ventricular dilatation at the time of diagnosis were also excluded.

Forty-two cases of fetal ventriculomegaly were observed between January 1987 and March 1998 at the Rouen University Hospital in France. In the 42 cases of fetal ventriculomegaly, only 26 were mild and isolated at the time of the initial scan and therefore considered eligible for inclusion in the study.

Follow-up prenatal tests included karyotyping, virological and haematologic studies of fetuses and mothers, as well as radiological investigation. Prenatal magnetic resonance imaging (MRI) was done in seven cases. Other prenatal tests were done in 17 cases: 17 viral investigations (maternal blood samples), ten amniocenteses for karyotyping and viral tests in fetuses, one cordocentesis (fetal blood count), 12 maternal haematologic studies (12 blood platelet counts and eight prothrombin time and activated partial thromboplastin time, four parental human platelet alloantigen genotypes).

Postnatal clinical examination, brain ultrasonography or MRI, electroencephalography and biological investigations were performed. Twenty had brain ultrasonography at birth, six had cerebral MRI above 6 months of age, three had viral investigations [three serology and one polymerase chain reaction (PCR) in neonatal blood], 12 had haematological tests (platelet count) and two karyotypes were also carried out.

The duration of clinical follow-up was a mean of 28 months (range 3 months–6 years).

RESULTS

Three groups of newborns were defined at birth (groups A, B and C). Group A included ten infants with regressive ventriculomegalies (these ventriculomegalies disappeared during pregnancy). Group B included ten infants with borderline ventriculomegalies (lateral ventricular atrial diameter was 10–13 mm during pregnancy and above the limit of normal values at birth without enlargment of ventricular cavities). Group C included six infants with confirmed ventriculomegalies at successive ultrasonographic prenatal and postnatal studies (lateral ventricular atrial diameter was 13–16 mm during pregnancy and ventricular dilatation was confirmed at birth). The most significant results are summarized in Table 1.

No major differences between the three groups in mean maternal age (28 years) was found. There was no consanguinity or significant previous family history.

Prenatal investigations

The mean maximal measurement of ventricular atrial diameter at diagnosis was higher in confirmed ventriculomegalies (14 mm in group C) than in others (10.8 mm in group A and 11.4 mm in group B, respectively). Regressive and borderline ventriculomegalies appeared earlier in pregnancy than the confirmed ventriculomegalies: mean gestational age at diagnosis was 25 weeks (18–31.5 weeks) in group A, 25.5 weeks (20–31 weeks) in group B and 30.5 weeks (21–37.5 weeks) in group C. Seventeen ventriculomegalies were bilateral, ten symmetrical, seven asymmetrical and nine were unilateral. The proximal hemisphere was clearly seen in all nine cases.

In each case the biparietal diameter was normal except in two fetuses in group C. In one case it was enlarged ($>$90th percentile) and the newborn was macrosomic, in another case it was reduced ($<$5th percentile) but head circumference at birth was normal.

During prenatal ultrasonographic follow-up, associated cerebral abnormalities were detected in three fetuses: a small cerebellum in group C, an intraventricular haemorrhage in group A and sub-ependymal cysts in group C. MRI subsequently confirmed ventriculomegaly but did not reveal other abnormalities. In two cases, a viral infection was suspected. In the first case in group C, a varicella virus infection was suspected because of a positive maternal serology at 25 weeks of gestation. This serology was not confirmed and PCR on amniotic fluid was negative. In the second case in group B, a parvovirus fetal infection was diagnosed as a positive PCR for parvovirus B19 was found in the amniotic fluid.

At birth

Postnatal clinical examination was normal in all but one case. One Down syndrome was discovered for a girl and confirmed by postnatal karyotyping in group B. In this instance, the parents had refused prenatal karyotyping. There were more boys than girls (sex ratio = 4.2). Twenty-three children were born at term and three were preterm.

Postnatal ultrasonography confirmed the prenatal ultrasonographic examination in all but four cases (three in group A and one in group B). Postnatal investigation revealed an additional abnormality in only one case in group C: the ventricular dilatation was associated with a porencephalic (parasagittal) cyst and hypoplasia of the corpus callosum. Alloimmune thrombocytopenia was suspected. In this case no prenatal MRI was carried out. Postnatal investigation confirmed the prenatal ultrasonographic diagnosis of sub-ependymal haemorrhage in group C and small cerebellum which was related to a Chiari malformation (type I) in group C. In this last case, prenatal MRI was not performed. Parvovirus infection was confirmed at 1 month by PCR in blood in group B. Varicella virus infection test was not carried out after birth in group C. Prenatal MRI was normal but postnatal MRI carried out at 7 and 20 months of age showed neuronal heterotopia in the white matter.

Table 1—Comparison between three groups of isolated ventriculomegaly

	Group A (10 regressive VM)	Group B (10 borderline VM)	Group C (6 confirmed VM)	Total (n = 26)
Maternal age (years)	19–36 (mean = 28.3)	21–40 (mean = 29.1)	21–40 (mean = 28)	19–40 (mean = 28.4)
Family history	1 pigmentary chorioretinitits	1 hydrocephalus	1 undefined chromosomal abnormality	3
Age of diagnosis (weeks of amenorrhea, WA)	18 = 31.5 WA (mean = 25 WA)	20–31 WA (mean = 25.5 WA)	21–37.5 WA (mean = 30.5 WA)	18–37.5 WA (mean = 27 WA)
Ventricular atrial diameter at diagnosis	10–13 mm (mean = 10.7 mm)	10–13 mm (mean = 11.4 mm)	11.5–15 mm (mean = 13 mm)	10–15 mm (mean = 11.7 mm)
Maximal atrial diameter during pregnancy	10–13 mm (mean = 10.8 mm)	10–13 mm (mean = 11.6 mm)	11.5–16 mm (mean = 11.6 mm)	10–16 mm (mean = 12.1 mm)
Bilateral VM	6	6	5	17
Prenatal examination				
Haematologic	2	6	4	12
Viral	6	7	4	17
Karyotype	0	4	3	7
MRI	0	4	4	8
Head circumference at birth	8 N 1 ≤ 3rd P, 1 = 10th P	5 N 4 ≤ 10th P (1 VLBW) 1 ≥ 90th P	2 N 1 ≤ 10th P (VLBW) 3 ≥ 90th P (1 macrosomia)	15 N 7 ≤ 10th P 4 ≥ 90th P
Sex: B/G	9/1	6/4	6/0	21/5
Postnatal clinical examination	9 N 1 TTS	9 N 1 Down syndrome	6 N	24 N 1 TTS 1 Down syndrome
Postnatal examinations				
Heamatologic	4	5	3 (1 AIT)	12
Viral	0	2	1	2
Karyotype	0	1 (Down syndrome)	0	1
EEG	1 (mild sufferance)	1 (N)	1 (PRSW)	1
US	7	7	6 (1 porencephaly, 1 cyst)	20
MRI	0	1	5 (1 cyst, 1 Chiari I, 1 small CC + cyst, 1 neuronal migration disorder)	6
Evolution				
Age	3 M–5 Y 11 M (mean = 28 M 1/2)	6 M–3 Y 3 M (mean = 29 M)	7 M–4 Y 3 M (mean = 26 M)	3 M–5 Y 11 M (mean = 28 M)
Lost to follow-up	3	1	0	4
HC	5N, 1 = −1 SD 1 = +1 SD	7 N, 2 = +1 SD 1 = +2 SD, 1 = −2.5 SD,	4 ≥ 2 SD, 2 ≥ 1 SD	12 N, 2 ≤ −1 SD 10 ≥ +1 SD
Neuromotor development	7N	1 = 8 N, 1 delay (Down syndrome)	3 N, 3 mild delay	18 N, 4 delay
Mean age for walking	12.8 months (12–14)	16.8 months (12–24)	19 months (14–24)	15.8 months (12–24)

AIT, Alloimmune thrombocytopenia; B, boy; CC, corpus callosum; EEG, electroencephalography; G, girl; HC, head circumference; M, months; MRI, magnetic resonance imagery; N, normal; P, percentile; PRSW, positive rolandic sharp waves; SD = standard deviation; US, ultrasonography; TTS, twin–twin transfusion syndrome; VM, vertriculomegaly; VLBW, very low birth weight; WA, weeks of amenorrhea; Y, year; ? = undefined.

Follow-up

Postnatal clinical follow-up was available for 22/26 infants. Average follow-up was 28 months (range 3 months–6 years).

Four children (15%) had a developmental delay. The first child in group B was a girl and her delay was related to Down syndrome. Three others were boys and had a mild delay. The second infant in group C, who had a suspected varicella infection during pregnancy and neuronal heterotopia in the white matter, had a large head circumference (+2.5 SD) and mild mental delay affecting language. Nevertheless, the child entered school at 3 years. The third infant in group C had a right parietal porencephaly which required a ventriculoperitoneal shunt at 7 and

Table 2—Comparison with studies in the literature for isolated ventriculomegaly[a]

Authors study period	Number of cases	Age of diagnosis (WA)	Ventricular atrial diameter (mm)	Prenatal evolution	Associated anomaly and aetiology	Birth term/ sex ratio	Follow-up	Characteristics of study. Method of psychomotor evaluation
Guillon (01/84–12/89)	18	26.5 WA (19.5–35)	$\geq$12 mm (12–22) bilateral and symmetrical VD and VL/H $<$0.6	17 stable 1 diminished	1 malformation discovered after birth	39.5 WA (36.5–41) Sex ratio $=$1.25	Follow-up from 3 years to 8 months (17 months–7 years) 1 HC + 3 SD 10 Brunet Lezine N 1 derivation 1 undefined total delay = 11.1%	Retrospective study 10 Brunet Lezine: N 17 clinical evaluation by pediatrician
Bromley *et al.* (02/87–05/90)	27	16–36 WA	10–12 mm	1 MIP	0	?	Follow-up from 3 to 18 months 21 N 5 handicapped = 7.6%	Retrospective study Clinical evaluation
Golstein *et al.* (1990)	13	24.2 $\pm$ 5.7 WA (15–38)	$\geq$10–$\leq$15 mm	9 deaths with 1 MIP 5 regressive (63%) 3 stables (37%) any increased	1 deficit in OCT at autopsy 1 cyst discovered after birth	?	3 neonatal delays 8 survived follow-up from 6 to 30 months: 6 N, 1 lost to follow-up and 1 delay (cortical cyst)	Retrospective study Clinical evaluation
Brown *et al.* (01/91–10/93)	14	?	11.5 mm (10–15)	8 regressive (57%) 2 stable (14%) 4 increased (28%)	1 Down syndrome	Sex ratio = 1	2 small HC $<$ 3rd P, 2 large HC $>$90th P 11 N, 3 delays (Down syndrome + 2 genetic history family) = 21%	Retrospective study Clinical evaluation
Alagappan *et al.* (1994)	11	?	$\geq$10 $\leq$13 mm	?	0	?	100% N 1 mild distal sacral agenesia	Retrospective study Clinical evaluation
Patel *et al.* (1994)	44 with 37 follow-up	26.5 WA (16–36)	11.66 mm (10–15)	10 regressive (38%) 16 stable (62%) 18 unprecised	10% associated and postnatal abnormalities with 2% chromosomal anomaly	32–41 WA Sex ratio = 3	1 neonatal death 34 survived 28 follow-up during 12 months with 72% N, 21% with delay	Retrospective study Clinical evaluation
Bloom *et al.* (01/90–02/96)	22	?	12.5 $\pm$ 2.1 mm	?	?	38.7 $\pm$ 1.9 WA Sex ratio = 1	8 delays (36.4%) with 2 regressive VM, 2 stable VM and 1 derivation	Randomised study in double blind

Table 2—Continued

Authors study period	Number of cases	Age of diagnosis (WA)	Ventricular atrial diameter (mm)	Prenatal evolution	Associated anomaly and aetiology	Birth term/ sex ratio	Follow-up	Characteristics of study. Method of psychomotor evaluation
Vergani *et al.* (01/90–12/96)	48	29 WA (16–35) and 13 <24 WA	≥10–≤15 mm (3 >12 and <14.9 mm).	2 deaths (1 MIP for Down syndrome, 1 unexplained death) 28 stables (58%), 10 regressive (33%), 4 increased (8%)	2 Down syndromes	Sex ratio=2.2	Follow-up from 30 months (3–72 months) Any delay in euploids	Prospective longitudinal study Clinical evaluation
Rouen (04/92–03/98)	26	27 WA (18–37.5)	12.1 mm (10–15)	11 regressive (42%) 8 stables (30%) 4 diminished (15%) 3 increased (11%)	1 Down syndrome, 1 Chiari, 2 suspected viral infections, 1 porencephaly, 2 ischaemic hemorrhages	38 WA (33–42) Sex ratio=4.2	Follow-up from 3 months to 6 years 4 lost to follow-up 4 delay (15.3%) 4 big HC at birth (≥90th P) 1 with derivation, epilepsy and neurovisual disorder	Retrospective study Questionnaires for parents and doctors, analysis of medical follow-up

[a]For each article, only mild isolated cases of ventriculomegalies are quoted in the table.
HC, Head circumference; MIP, medical interruption of pregnancy; N, normal; OCT, ornityl carbamyl transferase; P, percentile; VM, ventriculomegaly; WA, weeks of amenorrhea; ?=undefined.

13 months of age. This child had hemiparesis which did not impede walking, hemianopsia, epilepsy well controlled by anti-epileptic drugs and mild mental delay. The fourth child in group C had a Chiari malformation type I. At 20 months of age, he also had strabismus with growth acceleration (height and weight at +5 SD) and mild language delay.

DISCUSSION

In this study of 26 prenatal cases of isolated mild ventriculomegaly, the most severe ventriculomegalies were observed at a much later stage of gestation, a good prognosis in all but four cases, and a male preponderance.

Ventriculomegaly appeared at a later stage during pregnancy (group C) and may have been related to a pathological mechanism. In 3/6 cases in group C, an aetiology was found and developmental delay was observed. In two other cases, the head circumference was abnormal. Conversely, 19/20 regressive or borderline isolated ventriculomegalies could be physiological since prognosis was good in all but one case with Down syndrome.

Male preponderance has already been reported by Patel in 1994 (sex ratio = 3 in a study of 44 fetuses) (Patel *et al*., 1994) and Vergani in 1998 (sex ratio = 3.2 for isolated ventriculomegalies and 1.6 for associated ventriculomegalies) (Vergani *et al*., 1998). Two hypothesis could be proposed to explain these data. First, it could be an X-linked disease. However, we did not observe consanguinity or repetitive cases in the same family. A more plausible hypothesis could be a larger normal atrial diameter in boys. This is in agreement with Nadel *et al*.'s series (Nadel and Benacerraf, 1995) in which a difference of 0.4 mm between atrial diameter in boys and girls was observed. Vergani *et al*. (1998) stated that ventricular dilatation less than 12 mm could be a false positive in boys.

Prenatal investigation was often normal in mild cases of ventriculomegaly. Although postnatal tests confirmed ready all the prenatal investigations, two abnormalities were discovered after birth in two infants who were not thoroughly investigated during pregnancy: one infant in group B had Down syndrome and an other infant in group C had ventricular dilatation and porencephaly. Moreover, the fetus with the small cerebellum had Chiari malformation type I. Therefore, prenatal and postnatal tests should be carried out when there is persistent ventriculomegaly during pregnancy.

The developmental prognosis of infants with mild isolated ventriculomegaly appears favourable in the present series. In the four infants lost to follow-up, three had regressive ventriculomegaly in group A and one was borderline in group B. These infants probably had normal development. In the 22 other children, four had developmental delay with an established aetiology. One infant had Down syndrome in group B. The three others cases in group C had a mild delay with one suspected varicella infection, one porencephaly associated with a suspected alloimmune thrombocytopenia, and one Chiari malformation type I.

Therefore, in the present series, the risk of mental retardation only appears significant in group C with confirmed ventriculomegaly. In the literature (Table 2), a rate of mental delay between 0 and 36.4% was found in mild isolated ventriculomegaly (Guillon, 1991; Bromley *et al*., 1991; Golstein *et al*., 1990; Brown *et al*., 1995; Alagappan *et al*., 1990; Bloom *et al*., 1997). However, in all studies, the postnatal follow-up was short and the number of cases was small (11–44) (Table 2). Moreover, as in the present study, most of these series were retrospective and not standardized which may limit possible interpretations.

According to analysis of the present series and comparison with the literature, it appears that during pregnancy, if ventriculomegaly decreases, no other investigation is required. However, if ventriculomegaly is persistent, additional tests should be carried out. Amniocentesis must be performed for karyotyping and virological studies as well as maternal platelet count and virology. Fetal brain MRI should be performed between 28 and 30 weeks, to better assess the cerebral parenchyma and to investigate possible malformations, ie neuronal migration disorders or focal cortical dysplasias. If alloimmune thrombocytopenia is suspected (ventricular dilatation with intraventricular haemorrhage), maternal human platelet antibodies and alloantigen genotypes in both parents should be done.

After birth, brain ultrasonography and MRI must be performed in cases of persistent ventriculomegaly. If the ventricular atrial diameter is borderline, a routine clinical follow-up with a sonographic control should be sufficient. Finally, a long clinical follow-up should also be carried out (at least 6 years) to identify difficulties in school adaptability and attentional disorders.

CONCLUSION

The results of the present study suggest that prognosis of mild fetal isolated cerebral ventriculomegaly seems to be favourable. However, there is a risk of mental delay in cases of persistent ventriculomegaly and positive etiological investigations. From an ethical point of view, the results of the present series could be taken into consideration when advising patients about a possible prognosis of cerebral ventriculomegaly.

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