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Congenital hydrocephalus – prevalence, prenatal diagnosis and outcome of pregnancy in four European regions

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ABSTRACT

Objective: To describe prevalence, prenatal diagnosis and outcome for fetuses and infants with congenital hydrocephalus.

Methods: Data were taken from four European registries of congenital malformations (EUROCAT). The registries included are based on multiple sources of information and include information about livebirths, fetal deaths with GA ≥ 20 weeks and terminations of pregnancy for fetal anomaly (TOPFA). All cases from the four registries diagnosed with congenital hydrocephalus and born in the period 1996–2003 were included in the study. Cases with hydrocephalus associated with neural tube defects were not included in the study.

Results: Eighty-seven cases with congenital hydrocephalus were identified during the study period giving an overall prevalence of 4.65 per 10,000 births. There were 41 livebirths (47%), four fetal deaths (5%) and 42 TOPFA (48%). Nine percent of all cases were from a multiple pregnancy. Additional non-cerebral major malformations were diagnosed in 38 cases (44%) and karyotype anomalies in eight cases (9%). Median GA at TOPFA was 21 weeks. Among livebirths 61% were diagnosed prenatally at a median GA of 31 weeks (range 17–40 weeks) and median GA at birth was 37 weeks. Fourteen liveborn infants (34%) died within the first year of life with the majority of deaths during the first week after birth.

Conclusion: Congenital hydrocephalus is a severe congenital malformation often associated with other congenital anomalies. CH is often diagnosed prenatally, although sometimes late in pregnancy. A high proportion of affected pregnancies result in termination for severe fetal anomaly and there is a high mortality in livebirths.

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1. Introduction

Congenital hydrocephalus is characterized by an abnormal accumulation of cerebrospinal fluid (CSF) in the brain.[1] In the fetus and the infant the main clinical sign is enlargement of the head although in some cases with cerebral ventriculomegaly the head circumference is within normal limits. The CSF may be under pressure causing compression and damage to the brain. The reason for the accumulation of the CSF is an imbalance between production and absorption of the CSF. The most common causes of congenital hydrocephalus are obstruction of the cerebral aqueduct flow, Arnold Chiari malformation or Dandy–Walker malformation.[2]

In fetuses and infants the diagnosis of hydrocephalus is usually made following ultrasound scans. With the increasing number and quality of prenatal ultrasound investigations more cases are now diagnosed antenatally. The first prenatal signs of hydrocephalus may be visible on ultrasound around 18–20 weeks of gestation, the ''banana sign'' though in some cases the hydrocephalus is only visible later in gestation. Parents face difficult decisions on whether to continue or terminate the pregnancy when the diagnosis is made late in the second trimester and information on prognosis related to scan findings is lacking. For optimal counselling data on pregnancy outcome and childhood outcome in liveborn infants with congenital hydrocephalus are needed.

As congenital hydrocephalus is rare and because hydrocephalus also may be acquired after perinatal events (tumours, cerebral bleeding, CNS infections) publications give outcome data on these groups of infants together,[3] or include infants with spina bifida[4] or cover a long time period in order to have a reasonable number of cases.[5] Further published series only give data on liveborn infants referred for surgery.[4–6]

The aim of this study is to give the prevalence of congenital hydrocephalus in four European regions using population-based data from European Surveillance of Congenital Anomalies (EUROCAT) and describe prenatal diagnosis, outcome of pregnancy and mortality for the liveborn infants.

2. Materials and methods

EUROCAT registries are population-based and the geographically defined populations and methods of case ascertainment of EUROCAT are described elsewhere (http://www.eurocat.ulster.ac.uk/memberreg). The registries are based on multiple sources of information such as hospital records, birth and death certificates and post mortem examinations, and include information about livebirths (LB), fetal deaths (FD) with gestational age (GA) $\geq$ 20 weeks and terminations of pregnancy (TOPFA) after prenatal diagnosis of malformations. All structural malformations, syndromes and chromosomal anomalies are included in the database. Minor malformations are excluded according to an exclusion list. Malformations are coded according to ICD9/BPA or ICD10/BPA. The EUROCAT definition of hydrocephalus is: dilatation of ventricular system, not due to primary atrophy of the brain, with or without enlargement of the skull.

The four EUROCAT registries included in this study were Vaud (Switzerland), Oxford (UK), Funen County (Denmark) and Zagreb (Croatia). All cases born between 1996 and 2003 with a code for congenital hydrocephalus (ICD9, 7423 excluding hydranencephaly; ICD10, Q03) from the four registries were identified in the central EUROCAT database. Cases with associated neural tube defects were excluded from the study. Also cases with Dandy-Walker without hydrocephalus were excluded manually as the codes 74231 and Q031 code for Dandy-Walker both with and without hydrocephalus. All cases were checked to exclude cases with primary atrophy of the brain.

Available data in the database included sex, outcome of birth (liveborn, stillborn, termination of pregnancy), time of diagnosis, GA at discovery if prenatally diagnosed, age of mother and associated malformations. An additional questionnaire was filled in for each case with data on mode of delivery, induction of birth and indication, head circumference, description of diagnostic tests performed and, for liveborn infants, surgical procedures and outcome at 1 or 3 years of age.

The total number of births covered in the four regions 1996–2003 was 186,922.

Normal values for head circumference for comparison with study cases were taken from a recent Norwegian publication,[7] where the results were very similar to a British study published in 1994.[8] Head circumference values from the study came from direct measurements at birth or at termination, while the data for comparison is based on ultrasound studies.

3. Results

Fig. 1 shows the total number of cases pre- and postnatally diagnosed with outcome of pregnancy and survival.

3.1. *Prevalence and birth outcome*

Eighty-seven cases with congenital hydrocephalus were identified in the four EUROCAT registries during the study period giving an overall prevalence of 4.65 per 10,000 births (CI 3.77–5.74). Data on cases and prevalence by registry is presented in Table 1. Prevalence between regions differed significantly ($p < 0.05$). There were 41 livebirths (47%), four fetal deaths (5%) and 42 TOPFA (48%).

Median birthweight and GA for liveborn infants was low (median birthweight 2600 g and median GA 37 weeks). Nine percent of all cases (8/87) were from a multiple pregnancy. Seventy (80%) of the 87 cases were diagnosed prenatally. Of the 41 liveborn infants 61% were diagnosed prenatally. For those cases resulting in TOPFA median GA at prenatal diagnosis was 19 weeks; median gestation at prenatal diagnosis for livebirths was 31 weeks (Table 2).

For TOPFA cases median time interval from diagnosis to termination was 2 weeks. For prenatally diagnosed livebirths median GA at birth was 36 weeks compared to a median GA at prenatal diagnosis at 31 weeks.

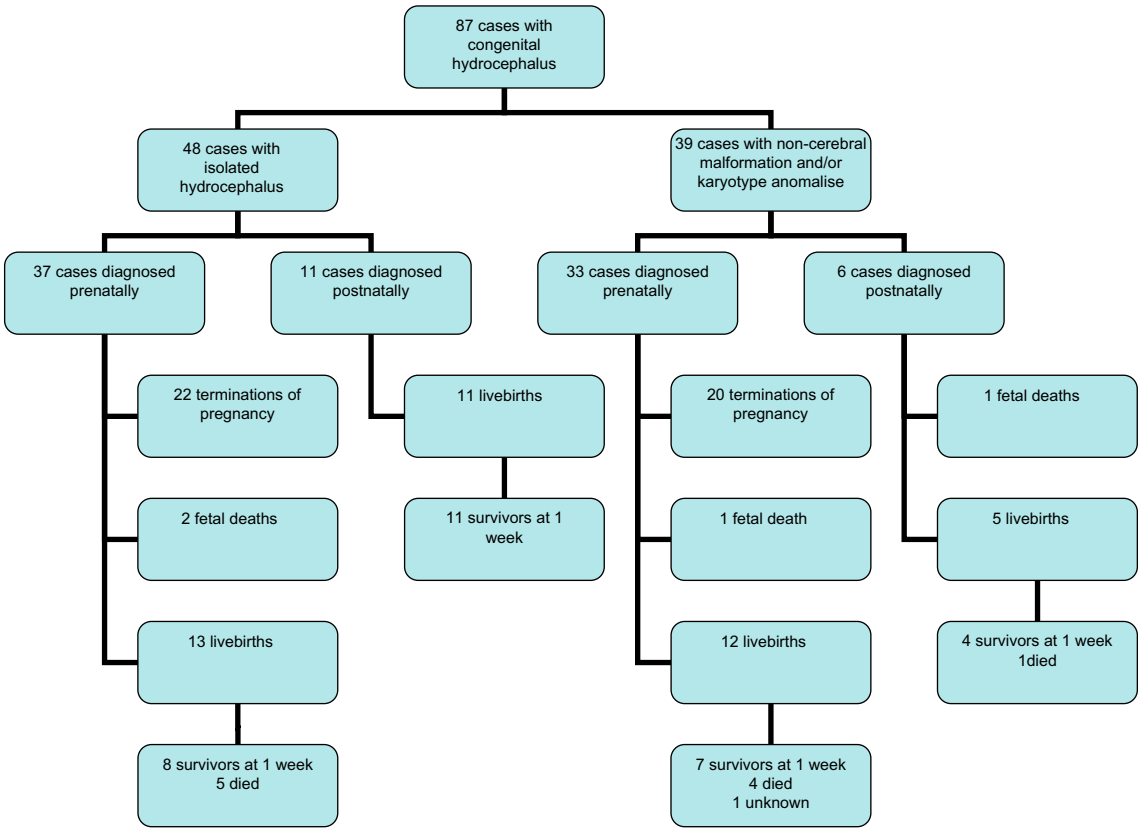

Fig. 1 – Flowchart for outcome of 87 cases with congenital hydrocephalus.

3.2. *Associated malformations*

Non-cerebral major malformations were present in 38 cases (44% of total) with the same proportion among livebirths, fetal deaths and TOPFA. Diagnosed syndromes and associated non-cerebral malformations are listed in Tables 3 and 4. The most frequent non-cerebral malformations were facial clefts, congenital heart disease and polycystic kidneys. Two cases were diagnosed with Fryns syndrome and two with Meckel–Gruber syndrome. In seven of these 38 cases there was an abnormal karyotype and a further one case had an abnormal karyotype with hydrocephalus as the only major malformation. Three cases had triploidy and the remaining five cases had different karyotype anomalies.

3.3. *Head circumference and mode of delivery*

Head circumference measured at birth, termination or at post mortem examination is presented in Fig. 2 and compared to published normal values.[7] It is evident that around half of all cases have a head circumference above normal limits at the time of birth or termination.

For livebirths there were only nine cases with a spontaneous birth and seven of these had a postnatal diagnosis of hydrocephalus. In 21 cases the birth was induced and for 11 cases induction of birth was not known. Mode of delivery was vaginal for 11 cases, planned cesarean section in 15 and acute cesarean section in eight cases (seven unknown).

Table 1 – Data on 87 cases congenital hydrocephalus by registry.

	Years included	Total births	Number of cases	Prevalence per 10,000 births (CI)[a]	Livebirths (% of total)	Fetal deaths (% of total)	TOPFA (% of total)
Vaud	1996–2003	58755	35	5.96 (4.28–8.30)	14 (40)	0	21 (60)
Oxford	1996–2002	41795	20	4.79 (3.09–7.41)	10 (50)	1 (4)	9 (45)
Funen County	1996–2003	44307	23	5.19 (3.45–7.81)	14 (61)	1 (4)	8 (35)
Zagreb	1996–2002	42065	9	2.14 (1.11–4.11)	3 (33)	2 (22)	4 (44)
Total		186922	87	4.65 (3.77–5.74)	41 (47)	4 (5)	42 (48)

a Confidence interval.

Table 2 – Characteristics of 87 cases with congenital hydrocephalus.

	Livebirths (N = 41)	Fetal deaths (N = 4)	TOPFA (N = 42)
Birthweight, median (range) (g)	2600 (633–4678)	1300 (1080–3700)	330 (25–1650)
GA, median (range) (weeks)	37 (28–41)	29 (24–33)	21 (14–31)
Boys/girls	21/18[a]	3/1	23/17[a]
Maternal age, median (range) (years)	30 (19–40)	34 (33–35)	30 (18–41)
Multiple pregnancy	3	0	5
Prenatal diagnosis (%)	25 (61)	3 (75)	42 (100)
GA at prenatal diagnosis, median (range) (weeks)	31 (17–40)	26 (20–32)	19 (13–30)
Non-cerebral malformations (%)	17 (41)	2 (50)	19 (45)
Karyotype performed (%)	16 (39)	2 (50)	29 (69)
Karyotype abnormal	0	0	8[b]

a Two unknown.
b Seven of these with non-cerebral malformations.

3.4. *Survival and surgery*

Thirty of 41 infants survived the first week of life. Ten infants died within the first week (1 week survival was unknown for one case), four infants died later in the first year of life giving a total first year mortality of 38% (14/37 as 1 year survival was unknown for four cases). Five of 24 infants (21%) without non-cerebral major malformations died within the first week compared to five of 16 infants (31%, one unknown) with non-cerebral major malformations ($p = 0.46$).

Data on surgery was only available from Switzerland and Denmark (28 livebirths). Surgery was performed on 16 infants of which two later died. Eight of the 16 children with surgery had one or more repeated operations performed within the first 3 years, mainly for shunt dysfunction. Surgery was not performed on 11 cases, three of whom were alive at 1 year. Of the remaining eight cases without surgery, seven died on the day of birth. Data on surgery was unavailable for one baby with multiple malformations who died 6 days after birth.

3.5. *Follow-up of survivors*

Follow-up of survivors was only available in Denmark. At 3 years of age four of the nine surviving children were found to have normal development for age. The five children that were not normal had mental retardation and/or cerebral palsy. Seven of the nine children were walking alone and a further one walking with aids. Overall of 23 cases with CH from Denmark, nine were alive at 3 years of age and four of these were normal for age.

Table 3 – Syndromes diagnosed in nine cases with congenital hydrocephalus.

Syndromes	LB	FD	TOPFA
Fryns syndrome			2
Meckel–Gruber syndrome	1		1
Noonan syndrome	1		
Crouzon syndrome	1		
Thanathoric dwarfism			1
Undiagnosed syndrome	2		

4. Discussion

Our study found a prevalence of CH at 4.65 per 10,000 births. Prevalence of CH (as defined in this study) has previously been reported to be 3.7 per 10,000 births in a Northern Region in the UK 1985–1996[9] and 8.1 per 10,000 births in Strasbourg, France 1979– 1987.[10] In the French study a large proportion of cases (29%) were diagnosed in infancy (after 1 week). As the

Table 4 – Non-cerebral major malformations diagnosed in 38 cases with congenital hydrocephalus, including malformations diagnosed in cases with syndromes and karyotype anomalies.

Associated anomalies	LB	FD	TOPFA
Eye	2		
Other malformations of face	2		
Cleft lip and palate	1		2
Cleft palate	1		4
VSD or ASD	3		2
Hypoplastic left heart			1
Pulmonary valve stenosis	1		
Ectopia cordis			1
Unspecified cardiac	1		
Coarctation of aorta		1	1
Patent ductus	1		
Lung cyst	1		
Diaphragmatic hernia			2
Abdominal cyst		1	
Anal atresia			1
Polycystic kidneys	2		4
Unilateral renal agenesis			1
Hydronephrosis bilateral	1		
Posterior urethral valves	1		
Horseshoe kidney			1
Omphalocele			2
Club feet			2
Syndactyly			2
Limb reduction defect			2
Polydactyly			1
Limb–body wall complex			1
Multiple malformations, unspecified	2		

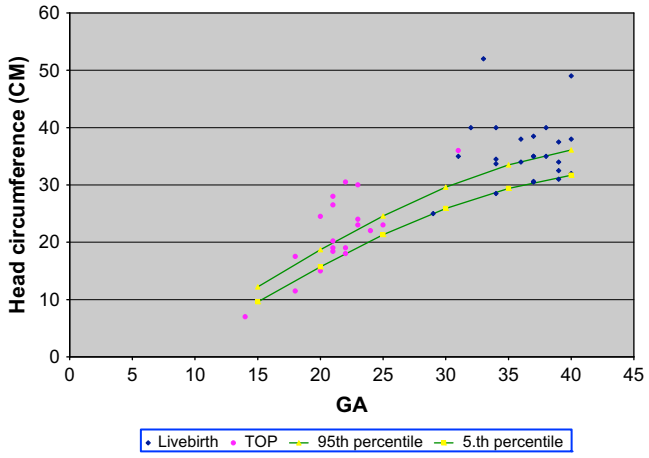

Fig. 2 – Head circumference in congenital hydrocephalus cases compared to 5th and 95th percentile according to reference (ref: Johnsen[7]).

definition of CH is broad without strict criteria for the size of the ventricles, prevalence may differ between studies. In our study difference in prevalence between regions was statistically significant, from 2.14 to 5.69 per 10,000 cases. All four registries are relatively small with good ascertainment of malformed cases.

The British study[9] showed a significant increase in total prevalence over time due to increased prenatal detection while the livebirth prevalence remained stable. Fetal deaths that previously remained undiagnosed may have been diagnosed prenatally and terminated. Livebirth prevalence in the French study (1979–1987) was 4.8 per 10,000 births, in the British study (1996–2003) 2.5 per 10,000 births compared to 2.2 per 10,000 births in our study (1996–2003). Terminations of pregnancy have approximately halved the livebirth prevalence of CH. Whether those prenatally diagnosed were more severe cannot easily be assessed.

We found a high proportion of associated malformations and karyotype anomalies (46%) among our CH cases. This high proportion of associated anomalies is comparable to what is found for omphalocele, where about half of the cases have associated anomalies.[11] Other studies of CH have also shown this high proportion of associated malformations and karyotype anomalies.[9,10] This emphasizes the importance of looking for other malformations after a prenatal or postnatal diagnosis of CH. Studies of major malformations of other organ systems have shown the impact of associated malformations and karyotype anomalies on birth outcome and survival.[12–14] In our study of a severe cerebral malformation the distribution of associated malformations was almost the same for those cases resulting in TOPFA and livebirths (45 and 41%) and there was no significant difference in 1 week mortality for livebirths with or without associated non-cerebral malformations. All cases with a karyotype anomaly were terminated.

Nine percent of our cases were from a multiple pregnancy, a proportion that is much higher than the normal twin rate of around 2% of all newborns. It has been described previously that hydrocephalus is significantly more frequent in twins[15] but the importance of our data is that it includes only CH whether diagnosed pre- or postnatally and thus excludes those hydrocephalus cases resulting from prematurity-related perinatal events. This finding is important in relation to the increasing number of multiple pregnancies in Europe due to assisted conceptions. Following prenatal diagnosis of a severe malformation in a fetus from a multiple pregnancy parents may request selective TOPFA for the affected fetus – a difficult ethical problem.

Eighty percent of all cases in our study were diagnosed prenatally and for livebirths the prenatal detection rate was 61%. There was a clear relation between GA at diagnosis and outcome of pregnancy as median GA for prenatal diagnosis for TOPFA cases was 19 weeks compared to 31 weeks for livebirths. Only seven of 25 liveborn cases were prenatally diagnosed before 28 weeks. This suggests that the timing of prenatal diagnosis may be the main criterion for deciding whether to terminate the pregnancy. Approximately half of our cases with CH had a head circumference within normal limits for GA suggesting that prenatal diagnosis by ultrasound is based on visualizing the dilatation of the ventricles and not on the size of the fetal head. We are not aware of other studies showing head circumference for CH cases at TOPFA or birth.

In our study cases were included if the hydrocephalus fitted with the EUROCAT definition: dilatation of ventricular system, not due to primary atrophy of the brain, with or without enlargement of the skull. None of the cases had borderline cerebral ventriculomegaly (width of ventricle $<$15 mm) noted on scan prenatally. Further we reviewed the cases from each registry reported with ''ventriculomegaly'' and we found no cases among them that at birth fulfilled our definition of hydrocephalus. Although the neurodevelopmental outlook for isolated borderline ventriculomegaly (normal karyotype, no associated malformations) is good if the measurement is $<$12 mm, it is less favourable when the ventricles measure $>$12 mm.[16]

Our study showed a poor prognosis for fetuses with CH. Only 47% of all cases were livebirths and of these 25% died within the first week after birth and at 1 year of age mortality was at least 38% (four infants with unknown infant survival). We are not aware of other studies on CH and survival for direct comparison with our data. Studies on disabilities in survivors with infant hydrocephalus of different etiologies have shown that more than half of all children have developmental or neurological problems.[4–6] The survival in our study is comparable to the survival published more than 20 years ago: one study on prenatally diagnosed CH including neural tube defects[17] and one study on CH overt at birth.[18] The literature further states that there is little or no correlation between the size of the ventricles and subsequent handicap.[19]

Further follow-up of the development and needs of children with hydrocephalus surviving infancy is needed. Data from European registries on cerebral palsy (SCPE) shows that CH is the second most frequent congenital malformation among children with CP.[20] Also investment in research on surgery for hydrocephalus to improve outcomes is recommended.

In conclusion CH is a severe congenital malformation, often diagnosed prenatally, although sometimes rather late in pregnancy and with a high proportion of associated

anomalies. Outcome is poor with a high proportion of pregnancies terminated for severe fetal anomaly and a high mortality in livebirths.

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