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Congenital microcephaly detected by prenatal ultrasound: genetic aspects and clinical significance

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ABSTRACT

Objective *The aim of this study was to analyze fetuses with prenatally diagnosed microcephaly including the nature of associated anomalies and the genetic-diagnostic implications.*

Design *Retrospective study design.*

Methods *A total of 30 fetuses with reliable dates and with prenatally diagnosed microcephaly as a common feature were analyzed.*

Results *Microcephaly was diagnosed at a mean gestational age of 28 weeks. More than half of the fetuses were also small for gestational age. Five subsets of microcephaly emerged from this study: (1) isolated microcephaly (16.7%); (2) microcephaly due to holoprosencephaly (16.7%); (3) microcephaly associated with chromosomal disorders (23.3%); (4) microcephaly as part of a genetic syndrome (20.0%); and (5) microcephaly as part of multiple anomalies (23.3%).*

Conclusions *In 25 out of 30 infants microcephaly proved to be part of a complex problem, emphasizing the need of a meticulous search for structural anomalies and fetal karyotyping when biometric data are not according to gestational age. The etiologic heterogeneity and variability of microcephaly in genetic syndromes are among the more difficult issues in prenatal ultrasound in pregnancies either with an incidental finding of this anomaly, or in cases with a recurrence risk. The complex situations described in this study demonstrate the importance of follow up, post-mortem investigation and careful genetic counseling.*

INTRODUCTION

Microcephaly is characterized by a small size of the brain as evidenced by an abnormally small head circumference and has an estimated incidence of 1 : 6200 to 1 : 8500 neonates[1–4]. The true incidence may be higher as the disorder often escapes detection in intrauterine death and stillborn infants.

The causes of microcephaly are heterogeneous and range from teratogenic, infectious, to multifactorial and chromosomal.

Microcephaly has been defined as a head circumference which is more than 2 SD below the mean[5] and by others as a head circumference of more than 3 SD below the mean[6].

The etiologic heterogeneity and variability of microcephaly in genetic syndromes are among the more difficult tasks in prenatal ultrasound imaging in pregnancies either with an incidental finding of this anomaly, or in cases with a risk of recurrence. This study presents a retrospective analysis of 30 cases of microcephaly including the genetic-diagnostic implications.

METHODS

Between 1 January 1990 and 1 January 1997, a total of 29 consecutive couples with prenatally established fetal microcephaly was seen in our centre. There were 30 affected fetuses, since in one couple there were two successively affected pregnancies. Referral indications for ultrasound investigation are presented in Table 1. Mean gestational age at the time of referral was 27 weeks (range 16–36 weeks). Pregnancy duration was established from a certain last menstrual period and/or fetal crown-rump length measurement ($n = 24$) during the first trimester of pregnancy. Mean maternal age was 28 years (range 19–37 years). Details on obstetric and familial history were noted.

Anomaly scans were performed on a Toshiba SSA 270 (carrier frequency 3.75 MHz). All data were related to normal reference charts according to Snijders and Nicolaides[7]. Microcephaly was defined as a fetal head circumference which was more than 3 SD below the

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Table 1 Prenatal detection of microcephaly: referral indications for ultrasound investigation

Reasons for referral	*n*
Reduced head size or suspected IUGR	16
Previous microcephaly	1
Intracranial abnormalities	5
Extracranial abnormalities	3
Hydrops	2
Polyhydramnios	1
Previous multiple abnormalities	1
Echodense bowel	1
Total	30

mean[6]. Selection did not take place on the basis of a postnatal diagnosis of microcephaly. A small for gestational age fetus was diagnosed when the fetal abdominal circumference was below the fifth centile of the reference curve[8]. Head circumference/abdominal circumference (HC/AC) ratio and head circumference/femur length (HC/FL) ratio were calculated.

Karyotyping was performed in 27 out of 30 (90%) fetuses by means of amniocentesis ($n = 17$), transabdominal chorionic villus sampling ($n = 4$) or cordocentesis ($n = 6$). In one infant the karyotype was determined by postnatal skin biopsy.

Decisions regarding obstetric management were based on structural ultrasound findings and fetal karyotype. The outcome of each pregnancy was documented. Information from the attending pediatrician, pathologist and/or geneticist regarding postnatal diagnosis was obtained in most cases.

Postnatally, the 30 infants were divided into five groups: isolated microcephaly (group 1), microcephaly due to holoprosencephaly (group 2), microcephaly associated with chromosomal disorders (group 3), microcephaly as part of a genetic syndrome (group 4) and microcephaly as part of multiple anomalies (unknown malformation syndrome; group 5).

Postnatally, genetic counselling was requested by 18 out of 29 (62%) couples.

RESULTS

Measurements of head circumference and abdominal circumference are shown in Figure 1a and b, respectively.

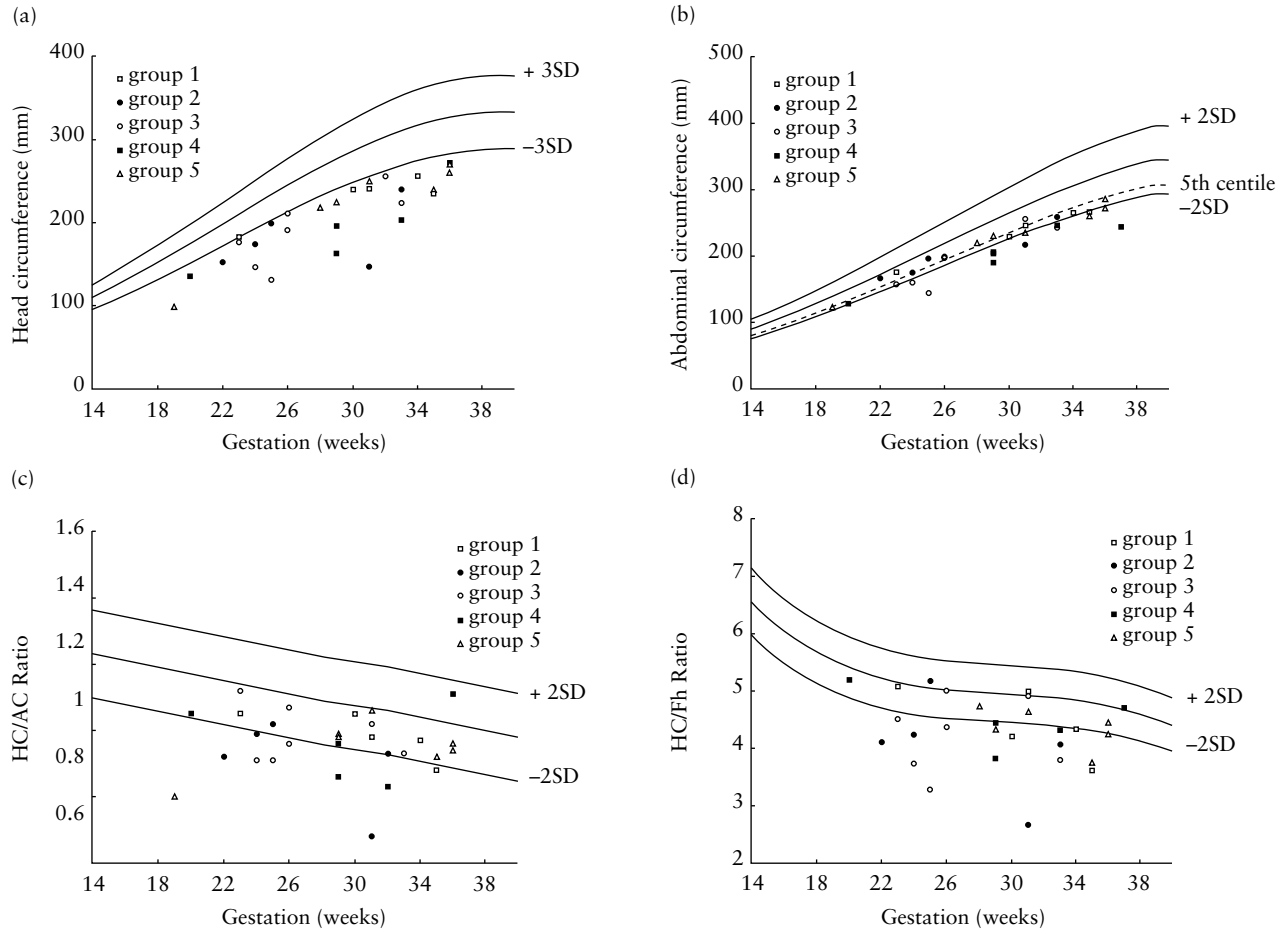

Figure 1 (a) Head circumference value obtained at first scan in 29 cases of microcephaly. (b) Abdominal circumference value obtained at first scan in 29 cases of microcephaly ($n = 29$). (c) HC/AC ratio obtained at first scan in 29 cases of microcephaly. (d) HC/FL ratio obtained at first scan in 28 cases of microcephaly. □, Group 1: isolated microcephaly; ●, Group 2: microcephaly caused by holoprosencephaly; ○, Group 3: microcephaly associated with chromosomal disorders; ■, Group 4: microcephaly as part of a genetic syndrome; ▲, Group 5: microcephaly as part of multiple anomalies (unknown malformation syndrome). HC/AC = head circumference/abdominal circumference; HC/FL = head circumference/femur length.

Table 2 Group 1: Isolated microcephaly

No.	*First anomaly scan (weeks)*	*Associated ultrasound anomalies*	*Fetal outcome (weeks), sex, weight (g)*	*Postnatal diagnosis*	*PM*	*Remarks*
1	35	Heart: dysplastic atrio-ventricular valves, abnormal hand/foot position	Alive, 43 F, 2810	Microcephaly		
2	30		Alive, 41 F, 2620	Microcephaly		Consanguinity of parents
3	31	Dilated posterior horns, abnormal	Alive, 38 M, 2105	Microcephaly		
4	23*	Ventriculomegaly, facial edema,	Alive, 38 M, 2300	Microcephaly†		
5	16*	Two vessel cord	TOP, 24 M, ?	Microcephaly	+	Previous child microcephaly

F = female; M = male; PM = postmortem investigation (+ performed); TOP = termination of pregnancy.
*Two or more ultrasound investigations in tertiary center.
†Unknown karyotype.

Calculated values of HC/AC and HC/FL are presented in Figure 1c and d, respectively. The fetal abnormalities diagnosed by ultrasound and the postnatal findings are presented in Tables 2–6.

Group 1: Isolated microcephaly

Prenatally, four out of five fetuses displayed minor ultrasound abnormalities.

Fetus no.4 developed microcephaly after its twin brother died *in utero* at around 23 weeks of gestation. This is probably an example of a twin-to-twin transfusion syndrome with ventriculomegaly and microcephaly being the result of severe hemodynamic changes after the death of the cotwin[9]. Karyotyping was not carried out in this pregnancy. The remaining fetuses all showed a normal karyotype. One pregnancy (no. 5) was terminated at 24 weeks of gestation. The parents of this fetus had had a previous child with microcephaly, who died at the age of 4 months. The consanguineous couple (no. 2) did not have previous infants (Table 2).

Group 2: Microcephaly due to holoprosencephaly

Microcephaly due to holoprosencephaly was present in five out of 30 cases (16.7%). A normal karyotype was present in all fetuses. Two pregnancies were terminated, three infants died after birth. Both consanguineous couples (nos 6 and 10) had healthy previous infants (Table 3).

Group 3: Microcephaly associated with chromosomal disorders

Chromosomal disorders were diagnosed in seven out of 30 cases (23.3%). Four pregnancies were terminated and two infants died after birth. In case no. 12, prenatal

Table 3 Group 2: Microcephaly due to holoprosencephaly

No.	*First anomaly scan (weeks)*	*Associated ultrasound anomalies*	*Fetal outcome, weeks, sex, weight (g)*	*Postnatal diagnosis*	*PM*	*Remarks*
6	20*	Holoprosencephaly, abnormal facial features, abnormal right ear	NND, 29 M, 1000	Holoprosencephaly, cyclops, absent nose, small mouth, abnormal ears†	–	IVF pregnancy; consanguinity of parents
7	31	Holoprosencephaly, hypotelorism, exophthalmus, cleft lip/palate	TOP, 31 M, 840	Holoprosencephaly, severe hypotelorism, absent nose, cleft palate, abnormal ears	–	
8	33	Holoprosencephaly, nuchal edema, hypotelorism, flat nose	NND, 36.5 F, 2300	Holoprosencephaly, median cleft lip/palate	–	
9	22	Holoprosencephaly, hypotelorism, absent nose, cleft lip, horse shoe kidney	TOP, 22.5 F, 432	Holoprosencephaly and facial anomalies as described	–	
10	25	Holoprosencephaly, cleft lip, hypoplastic nose, stomach not visible	NND, 37 M, 1725	Holoprosencephaly, hypotelorism, flat nose, abnormal ears, bilateral cleft lip/palate		Consanguinity of parents

F = female; M = male; PM = postmortem investigation (– not performed); NND = neonatal death; TOP = termination of pregnancy; IVF = *in-vitro* fertilization.
*Two or more ultrasound investigations in tertiary center.
†karyotyping by skin biopsy.

Table 4 Group 3: Microcephaly associated with chromosomal disorders

No.	*First anomaly scan (weeks)*	*Associated ultrasound anomalies and karyotype*	*Fetal outcome, weeks, sex, weight (g)*	*PM*	*Remarks/postnatal diagnosis*
11	24	Oligohydramnios, intracranial anatomy not seen, no bladder filling, kidneys not visible 46,XY,der(7)t(7; 12)(q34; p13) paternal	TOP, 26 M,?	+	PM; holoprosencephaly, cyclopia, proboscis, cardiac abnormality
12	26*	Right-sided hydronephrosis; 31 weeks: microcephaly 46,XY,del(7)(q34)	NND, 37 M, 2250	–	Micrognathia, broad nasal bridge, short neck bell-shaped thorax, hydronephrosis, megaureter
13	25	Hypotelorism, exophthalmus, thickened myocardium, short ulna/radius 47,XY, + 8[4]/46,XY[61] in fetal blood	TOP, 26.5 M, 375	–	Ventriculomegaly, large ears, exophthalmus, small cleft lip, choanal stenosis/atresia, abnormal lower arms and hands
14	33	Ventriculomegaly, two vessel cord 46,XX, + 13,der(13; 14)(p11; q11), de novo	NND, 36 F, 1780	+	PM: holoprosencephaly, ventricular septal defect, polydactyly, cleft lip/palate, abnormal ears
15	26	Holoprosencephaly, hypotelorism, left/right heart asymmetry 47,XY, + 13	TOP, 29 M, 1075	–	Abnormal skull, hypotelorism, one nostril, polydactyly (fingers)
16	23	Holoprosencephaly, cleft lip, echodense kidneys, ambiguous genitalia, left/right heart asymmetry 47,XY, + 13	TOP, 25 M, 490	?	No information
17	26	Abnormally shaped cavum septum pellucidum, bilateral cleft lip, ambiguous genitalia, dysplastic heart valves, abnormal kidneys 46,XY, + 13,der(13; 14)(q10; q10) paternal	IUD, 34 weeks 37, M?	–	ICSI pregnancy, consanguinity of parents, no post mortem examination (maceration)

F = female; M = male; PM = post mortem investigation (+ performed, – not performed); TOP = termination of pregnancy; NND = neonatal death; IUD = interauterine death; ICSI = intracytoplasmic sperm injection.
*Two or more ultrasound investigations in tertiary center.

karyotyping initially revealed a normal karyotype. However, postnatal rekaryotyping demonstrated a deletion 7q34. In one twin pregnancy established by intracytoplasmic sperm injection (ICSI), a translocation trisomy 13 was found in the fetus with microcephaly (no. 17) while a balanced Robertsonian translocation was present in the other normally developing fetus. The father was subsequentially found to be carrier of a balanced Robertsonian translocation 45,XY,der(13;14)(q10;q10)[10]. The fetus with microcephaly died *in utero* at 34 weeks of gestation (Table 4).

Group 4: Microcephaly as part of a genetic syndrome

A genetic syndrome was diagnosed in six out of 30 infants (20.0%). Normal karyotypes were presented in all cases.

In one fetus (no. 23), being a sib of an infant (no. 22)

Table 5 Group 4: Microcephaly as part of a genetic syndrome

No.	*First anomaly scan (weeks)*	*Associated ultrasound anomalies*	*Fetal outcome, weeks, sex, weight (g)*	*Postnatal diagnosis*	*PM*	*Remarks*
18	24*	Olioghydramnios, two vessel cord 37 weeks; microcephaly	Alive 38, F, 1700	Cornelia de Lange syndrome		
19	29	Craniosynostosis, hypotelorism, micro/retrognathia, abnormal hand/foot position, no movements	NND 32, M, 1050	Fetal akinesia syndrome	–	
20	29	Craniosynostosis, dilated posterior horns, cerebellar abnormality	NND 38, F, 1430	Seckel–like syndrome	+	Consanguinity of parents
21	27*	Hypoplastic cerebellum, micro gnathia, pes equinovarus, echodense lens, small stomach	NND 42, F, 1400	Neu–Laxona syndrome	+	Consanguinity of parents
22	29	Hypertelorism, micrognathia, arms: flexion contractures, legs: extension contractures, no movements	NND 32, M, 890	Pena Shokeir type 1	+	Consanguinity of parents, sib of patient 23; previous child Fragile X syndrome
23	18*	Corpus callosum agenesis, hypoplastic cerebellum, echodense lenses, micrognathia, generalized skin edema, no movements	TOP 23, M,?	Pena Shokeir type 1	+	Sib of patient 22

F = female; M = male; PM = postmortem investigation (+ performed, – not performed); NND = neonatal death; TOP = termination of pregnancy.
*Two or more ultrasound investigations in tertiary center.

Table 6 Group 5: Microcephaly as part of multiple anomalies (unknown malformation syndrome)

No.	*First anomaly scan (weeks)*	*Associated ultrasound anomalies*	*Fetal outcome (weeks), sex, weight (g)*	*Postnatal diagnosis*	*PM*	*Remarks*
24	35	Oligohydramnios, abnormal right hand position, ventricular septal defect	Alive 39, F, 1830	Bilateral microcornea, ventricular septal defect, pulmonary atresia, persistent ductus arteriosus		
25	29	Small cavum septum pellucidum, left/right heart asymmetry, dysplastic valves, left pesequinovarus	Alive 29, M, 2690	Pes equinovarus left, cardiac abnormality		IVF pregnancy
26	19	Hydrops, hygroma colli, stomach not filled, contractures, no movements	TOP 20,?	Arthrogryposis associated with microcephalia vera	+	
27	28	Caudal vermis defect, large cisterna magna, micrognathia, double outlet right ventricle, stomach not filled, abnormal hand position	IUD 29, M. 1100	Micrognathia, hypertelorism, low set ears, webbed neck, rocker bottom feet		
28	24*	Ventriculomegaly, micrognathia, nuchal oedema, left diaphragmatic hernia, pectus excavatum, double outlet right ventricle, overlapping fingers	NND 33, M, 1580	Low set ears, hypo/epispadia		
29	36	SGA; right/left heart asymmetry	Alive 38, F, 1935	Porencephalic cyst†		
30	20.5*	Echodense bowel; 34 weeks: abnormal intracranial anatomy?	Alive 38, M, 2390	Ventriculomegaly, mega cisterna magna, hypoplastic cerebellum, hypertelorism, microspheraci, low set right ear, small thorax, wide spaced nipples, small penis		Consanguinity of parents

F = female; M = male; PM = postmortem examination (+ performed, – not performed); TOP = termination of pregnancy; NND = neonatal death; SGA = small-for-gestational age; IVF = *in-vitro* fertilization.
*Two or more ultrasound investigations in tertiary care.
†unknown karyotype.

with Pena Shokeir syndrome type 1, a recurrence of this syndrome was diagnosed by ultrasound. This pregnancy was terminated. Prior to ultrasound investigation, prenatal cytogenetic and DNA investigations were carried out in both cases, turning out normal, because the mother was a carrier for FMR-1 (fragile X) mutation. These investigations were normal in both cases.

Four infants died in the neonatal period. One infant with a postnatally diagnosed Cornelia de Lange syndrome (no. 18) is alive (Table 5).

Group 5: Microcephaly as part of multiple anomalies

In seven cases microcephaly combined with other anomalies did not match with known syndromes. Karyotyping was not carried out in patient no. 29. All other fetuses showed normal karyotypes. One pregnancy was terminated, one infant died in the neonatal period. Three infants are alive (Table 6).

Diagnosis

Overall, in this study (group 1–5) microcephaly was diagnosed at a mean gestational age of 28 weeks (range 18–36 weeks). The fetal abdominal circumference was below 2 SD in 19 out of 29 fetuses (Figure 1b; 66%), suggesting that more than half of the fetuses were also small for gestational age. Doppler flow measurements of the umbilical artery were performed in nine fetuses and were found to be normal, ruling out placental insufficiency.

The birth weights of 25 out of 30 infants are shown in Tables 2–6. In 16 out of 25 (64%) infants, birth weight was < -2 SD and in 40% (10 infants) < -3 SD of the mean, proving growth retardation.

The overall mortality rate was 70% (21 out of 30 infants), of which 43% (nine out of 21 infants) was represented by pregnancy terminations. Nine infants (30%) are alive; all are mentally retarded.

Post-mortem investigation was performed in eight out of 21 (38%) fetuses/infants.

DISCUSSION

In the present study, a heterogeneous group of 30 affected infants is presented with prenatally diagnosed microcephaly as a common feature. Prenatal diagnosis consisted of a fetal head circumference at or below -3 SD of the mean. Head circumference measurements even slightly less than -3 SD turned out postnatally to be microcephalic. This may be partly due to selection, since all small for gestational age fetuses with abnormal Doppler findings were excluded from this study. Sloping of the forehead was seen in most cases of microcephaly. Since data were collected over a 7-year time period, no information was available on a possible deviation in normal blood flow to the fetal brain, as recently described by Pilu *et al.*[11] In five

cases isolated microcephaly was established postnatally; minor associated anomalies, suspected prenatally in three cases, were not confirmed after birth. In the remaining 25 out of 30 (83%) infants, microcephaly proved to be part of a complex problem, emphasizing the need for a meticulous search for structural anomalies and fetal karyotyping when biometric data are not according to gestational age.

In the presence of microcephaly one would expect the HC/AC ratio to be reduced. However, 19 out of 29 (66%) HC/AC ratio values (Figure 1c) and 10 out of 28 (36%) HC/FL ratio values (Figure 1d) were situated within the normal range (above −2 SD). This is due to the reduced abdominal circumference (< 5th centile) in 19 out of 29 (66%) cases reflecting the presence of an SGA fetus. This high percentage of SGA fetuses may be determined by the referral pattern in this study. Approximately half of the cases were referred to our centre because of abnormal fetal biometry, suggesting abnormal fetal growth.

Microcephalic infants have brains which are not only small, but may also be dysmorphic as expressed by the presence of holoprosencephaly ($n = 6$) and cerebellar abnormalities ($n = 6$), the latter ranging between hypoplastic cerebellum ($n = 4$) and caudal vermis defect ($n = 2$). Facial anomalies (hypotelorism, exophthalmus, abnormal/absent nose and cleft lip/palate) were nearly always associated with holoprosencephaly.

An abnormal fetal karyotype was established in seven out of 30 pregnancies (23.3%), of which five represented a euploid chromosomal abnormality. Structural anomalies included central nervous system, facial, cardiac and genitorenal anomalies.

Genetic counseling was requested by 18 out of 29 (62%) couples (infants 22 and 23 are sibs). The mother of pregnancies 22 and 23 was a carrier of the fragile X syndrome. After exclusion of this diagnosis in the fetus in her second pregnancy by chorion villus sampling, an eventual diagnosis of the autosomal recessive Pena Shokeir syndrome type 1 was made. The third pregnancy was found to be affected by the 18th week.

The recurrence risk of the remaining four genetic syndromes was counseled to be sporadic (no. 18), 20% (no. 19) or autosomal recessive (nos 20 and 21).

Finally, infant 30 resulted from a first pregnancy of a consanguineous couple (first cousins) suggesting an autosomal recessive mode of inheritance although the infant showed sonographic signs of a possible viral infection during pregnancy (hyperechogenic bowel; oligohydramnios).

The complex situations described above demonstrate the need for careful follow up studies, post mortem investigation and genetic counseling. All parents were counseled prenatally based on the available information at that time. They were informed about the importance of postnatal evaluation that included determination of the recurrence risk of fetal pathology. It is striking that only 57% (12/21) gave permission for post-mortem investigation and also that only 60% consulted a clinical geneticist. This may be explained by different cultural backgrounds.

When microcephaly is part of a syndrome or sequence, prenatal diagnosis in a subsequent pregnancy should not be based on the detection of microcephaly because in many cases this feature will only become apparent during the late second or third trimester. A syndrome or sequence including microcephaly should therefore rather be based on other features, such as central nervous system, facial, cardiac and renal anomalies, which can be recognized in the late first or early second trimester of pregnancy. Unfortunately, a recurrence of isolated microcephaly cannot always be detected before fetal viability due to the relative late slowing of fetal head growth and variable expression of this anomaly.

The perinatal mortality rate was 70% (21/30), with half of the deaths occurring in the neonatal period. Of the 10 infants that remained alive, four presented prenatally with isolated microcephaly.

In summary, in the present study approximately half of the pregnancies were referred for reasons other than suspected microcephaly. These data therefore relate to a selected subset of microcephalic infants. Perinatal mortality was determined by the severity of associated anomalies rather than by microcephaly alone. In chromosomally normal cases the recurrence risk of microcephaly varies depending on the presence of associated anomalies or syndromal pathology, the latter mostly following an autosomal recessive inheritance pattern.

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