Congenital Anomaly Register & Information Service

caris review

including 1998-2005 data

inside...

NHS WALES GIG CYMRU

online ar-y-we CARIS

CARIS, the Congenital Anomaly Register and Information Service for Wales, is based at Singleton Hospital, Swansea. It is funded by the Welsh Assembly Government and is part of NHS Wales.

Foreword

Welcome to the 2005 CARIS annual review. This year our special articles focus on major anomalies of the central nervous system.

Detailed data tables are available from the CARIS website on www.wales.nhs.uk/caris

We would like to express our sincere thanks to all contributing health professionals for their continuing support.

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The CARIS team at the 2005 South Wales Annual Meeting.

We are (left to right) David Tucker, Debbie Rogers, Helen Jenkins, Margery Morgan, Val Vye, Judith Greenacre.

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* also accessible through the HOWIS (NHS Wales) website at www.howis.wales.nhs.uk/caris

What is CARIS?

CARIS aims to provide reliable data on congenital anomalies in Wales. These data are used to assess:

- **patterns of anomalies in Wales**
- **antenatal screening / interventions**
- **health service provision for affected babies and children**
- **possible clusters of birth defects and their causes**

We collect data on any baby or fetus for whom pregnancy ended after 1st January 1998, where the mother is normally resident in Wales at the end of pregnancy.

CARIS uses a multiple source reporting system and, at present, over 100 individuals or agencies regularly send us information. Data from clinical and laboratory sources is reported via warning cards, reporting forms and data exchanges. CARIS co-ordinators in each trust are responsible for much of the clinical reporting (details available from our website). In the CARIS office, data are collated, information is coded and quality carefully checked. The data are then available for feedback to clinicians – paediatricians, ultrasonographers, midwives, etc. We also supply information to the National Assembly for Wales, EUROCAT, International Clearing House for Birth Defects and the Office for National Statistics (NCAS) for surveillance.

We cannot overemphasise the importance we give to data confidentiality. We operate a strict security and confidentiality policy and have gained support under Section 60 of the Health and Social Care Act 2001. This means that the register can continue collecting and analysing data.

CARIS has set up an Expert Advisory Group to advise on future developments and monitor progress of the register.

Over 37,000 recorded pregnancies occur in Wales each year. Of these, about three quarters are registered as live or still births, the rest ending in termination or spontaneous loss of the fetus before the 24th week of pregnancy. About 3% of births take place at home. Wales has 13 consultant obstetric units and 10 midwifery led units. The majority of births take place in these units. However, a significant number of births to Welsh mothers occur in English hospitals. Good links with congenital anomaly registers that border Wales (Mersey, West Midlands and the South West of England) remain very important.

Clinical reporting is the most important source of information for CARIS, especially for those babies who:

- **die but do not have a post mortem**
- **survive and have anomalies not requiring immediate specialist help.**

Diagnostic services, particularly ultra sound and pathology, can alert us to a case or give valuable further information.

Regional specialist services, including cytogenetics, can help by providing more details of the anomalies involved.

We also link to other databases, such as PROTOS (Cardiff), the All Wales Perinatal Survey and the Standard Child Health Computer System.

Key points on congenital anomalies in Wales 1998-2005

- 12,149 cases with confirmed congenital anomalies have been reported to CARIS with pregnancy ending between 1st January 1998 and the 31st December 2005. These include live births, stillbirths, terminations of pregnancy for congenital anomalies and miscarriages (although reporting of miscarriages will inevitably be incomplete). This means that the gross* rate of known pregnancies affected by congenital anomaly is 4.8%.
- 85% of cases were live born. The percentage of all live born babies affected by congenital anomalies is 4.0%. CARIS makes every effort to ensure that babies who die during the first year of life are identified. According to our records, over 96% of live born babies with a congenital anomaly survived to the end of their first year of life. This percentage is higher than we have reported in previous years, probably as a result of increased availability of data on survivors from inpatient hospital records and community child health computer systems.
- In over half of cases only one birth defect was recorded. In about 12% of cases an underlying chromosomal disorder was identified that could account for many of the physical anomalies. The remainder of cases had multiple anomalies of varying levels of complexity.
- As in previous years defects of the heart and circulation were the largest single group of anomalies, followed by defects of the limbs, urinary system and musculoskeletal system.
- Overall rates of congenital anomaly continue to be higher in male babies.

*The gross rate includes all cases of anomaly recorded as miscarriages, terminations of pregnancy, live and stillborn babies

- As before, marked variations in congenital anomaly rates are seen around Wales, with apparently much higher rates for Swansea and Neath Port Talbot compared to other areas. Relatively lower rates are seen in, Mid Wales and parts of North Wales. Some of this variation remains due to persistent differences in reporting practices across Wales (See Reporting of anomalies in Wales: CARIS Review 2003). The areas with highest rates tend to have better survival rates for live born babies. This may, again, reflect better reporting of cases in infancy, allowing more survivors to be added to the numbers from better reporting areas.
- Rates for many anomalies in Wales appear relatively high when compared to other areas of Britain and Europe. This was also discussed in detail in the 2003 CARIS review. We still suspect that good reporting in Wales accounts for a large part of these differences but continue to keep the situation under review.
- Data tables and a more detailed commentary are available on the CARIS website.

Summary

- Gross* rates of congenital anomalies reported is 4.8%.
- 85% of cases are live born.
- 96% of live born cases survive to the end of their first year.
- Heart and circulatory defects are the largest single group.
- Variations in rates exist around Wales.
- Congenital anomaly rates in Wales are often apparently higher than for other areas of Europe or Britain.

CARIS activity 2005

The team has been involved with projects in Wales, the United Kingdom and internationally.

Wales

- Annual meetings were held in Ysbyty Glan Clwyd and the National Botanical Gardens near Carmarthen. The focus was on gut anomalies.
- CARIS continued to collaborate with Antenatal Screening Wales supporting development of the new antenatal ultrasound module of RADIS (radiology information system) and a population based ultrasound soft marker study.
- CARIS developed new sources of data, including inpatient data from Alder Hey Hospital, relating to North Wales.

United Kingdom

BINOCAR:

- CARIS gave presentations on gastroschisis and clinical coding of anomalies at the annual meeting. David Tucker was appointed as chairman of the clinical coding working group.

International

- Gastroschisis and hypospadias data were presented at the EUROCAT (European Collaboration of Congenital Anomaly Registers) conference in Poznan, Poland in June 2005.
- CARIS became a full member of the International Clearing House of Birth Defects, Surveillance and Research (ICBDSR)
- We presented Welsh data on anomalies associated with maternal anti-depessants (SSRIs) at ICBDSR conference in Malta in September 2005.

Websites

- www.binocar.org.uk
- www.eurocat.ulster.ac.uk
- www.icbdsr.org

Neural Tube Defects

This report was originally prepared by Siobhan Jones, Specialist Trainee in Public Health, National Public Health Service for Wales.

A neural tube defect is a major congenital anomaly caused by abnormal development of the neural tube.
The neural tube is the structure present during embryonic life which gives rise to the central nervous system – the brain and spinal cord. Neural tube defects (NTDs) are among the most common anomalies that cause infant death and serious disability.

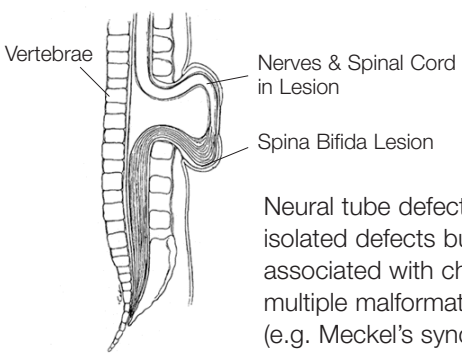
There are different types of neural tube defects which include anencephaly, spina bifida, and encephalocele.
In anencephaly there is absence of the cranial vault (skull) and absence of most or all of the cerebral hemispheres of the brain. Encephalocele is a hernia of part of the brain and meninges (the membranes covering it) through a skull defect. Spina bifida is an opening in the vertebral column encasing the spinal cord (figure 1).

436 cases of neural tube defect were reported to CARIS between 1998 - 2005. Of these:

- **185 had anencephaly**
- **204 had spina bifida**
- **55 had encephalocele**

(some cases have more than one type of NTD)

figure 1: diagram showing a spina bifida defect

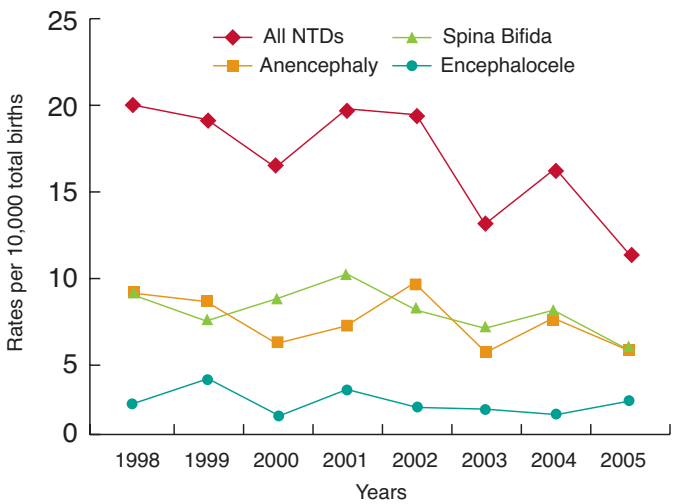


Neural tube defects usually occur as isolated defects but may also be associated with chromosomal or other multiple malformation syndromes (e.g. Meckel's syndrome).

Picture of neural tube defects in Wales

Historically, the recorded prevalence of neural tube defects in Wales has been higher than elsewhere[1]. A 1957 South Wales study reported a rate of 115 neural tube defects per 10,000 births[2].
Subsequent studies suggest that the rate has declined. A 1992 study reported a rate of 21 per 10,000 total births, although this only covered parts of South Wales[3].
Data since CARIS was established show an all Wales prevalence rate of 17.1 per 10,000 total births for the period 1998-2005 (95% CIs 15.5 to 18.7). The CARIS rate for south east Wales for this time period is 16.3 (95% CIs 14.0 to 18.6).
The geographical areas studied are different to earlier research making direct comparisons difficult. There is some evidence of a downward trend since 1998 (figure 2).

figure 2:
Time trend for neural tube defects in Wales (1998 – 2005).
Source: CARIS



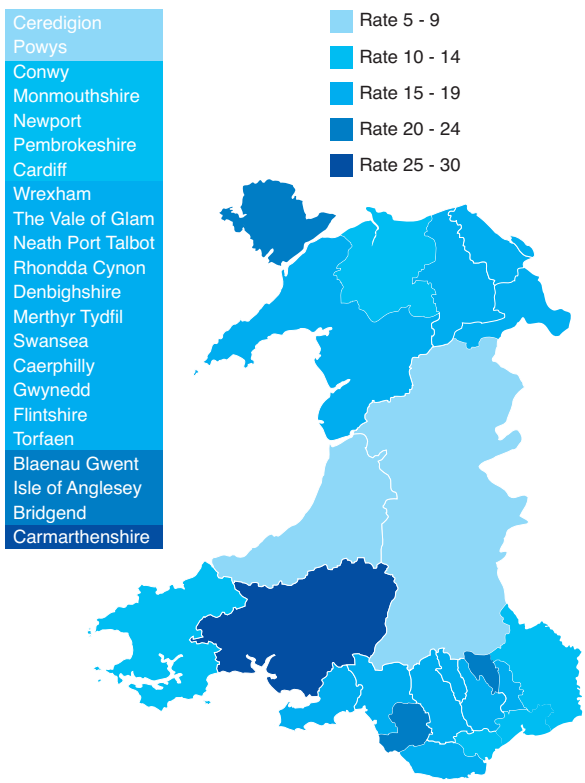
[1] Folic acid and the prevention of neural tube defects. DOH 1992
[2] Laurence KM. The apparent declining prevalence of neural tube defects in two counties of South Wales. Z Kinderchir 40 supplement I: 58-60 (1985)
[3] Wales participation in the EUROCAT surveillance of congenital abnormalities: a report of the study in South Glamorgan and Gwent during 1992 (draft). Cotter M. Elder S, Laurence KM. WHCSA March 1994

Neural Tube Defects

At local authority level, there are marked differences in rates across Wales, that are not explained simply by known patterns of variations in reporting. Rates are generally higher in the north and south with much lower levels in mid Wales, although, at regional level, these differences are not statisically significant. Carmarthenshire has the highest rate of neural tube defects, significantly higher than that for Wales as a whole. This may be a chance finding, but CARIS will work with others to investigate this further over the coming year.

figure 3:
Rates of neural tube defects by Unitary Authority (1998-2005)

Source: CARIS

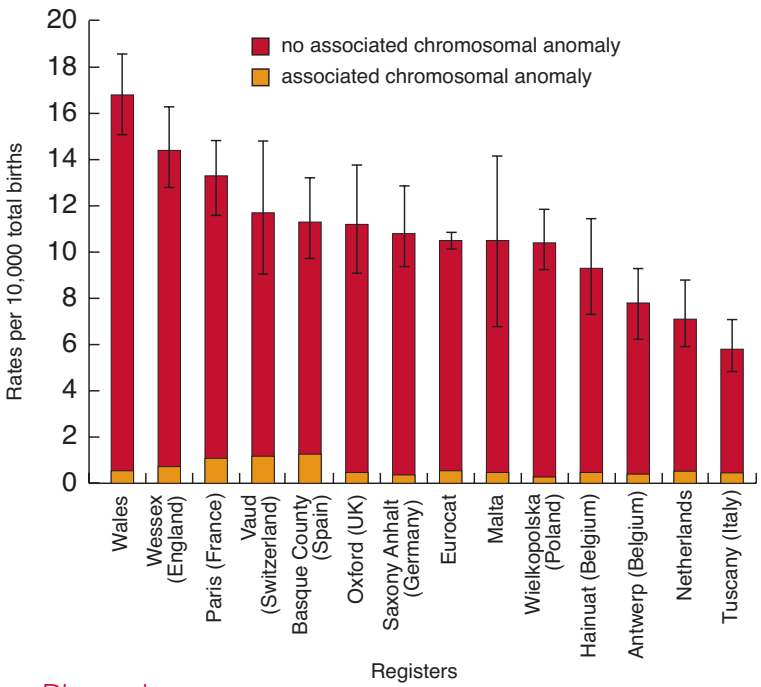


Wales and Europe

Wales has one of the highest rates of neural tube defects reported in Europe. (Bulgaria reports higher rates, but data is not complete for comparable years to CARIS).

figure 4:
Rates of isolated NTD in Europe (1998-2004): Highest reporting registers submitting complete data.

Source: EUROCAT



Diagnosis

Ultrasound

Ultrasound screening is very effective at detecting neural tube defects. A systematic review of the effectiveness of ultrasound screening reported a detection rate for all neural tube defects of 76.4% on routine second trimester ultrasound scan.
The detection rate for anencephaly is reported as 97.4% and 66.7% for spina bifida.

Neural Tube Defects

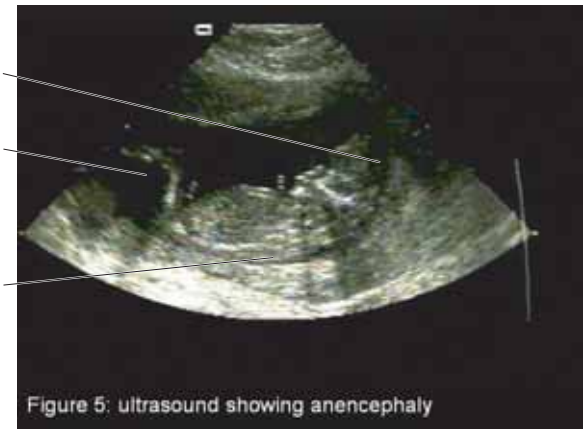


Figure 5: ultrasound showing anencephaly

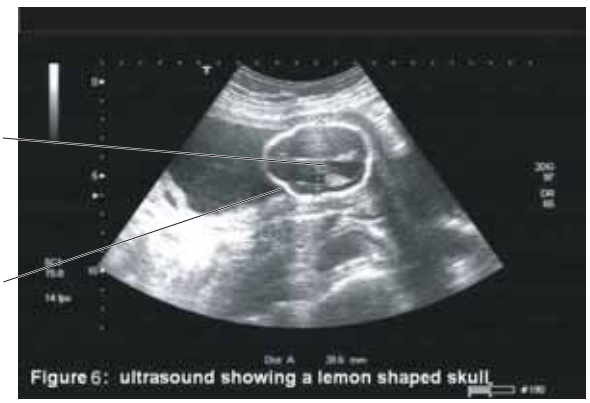


Figure 6: ultrasound showing a lemon shaped skull

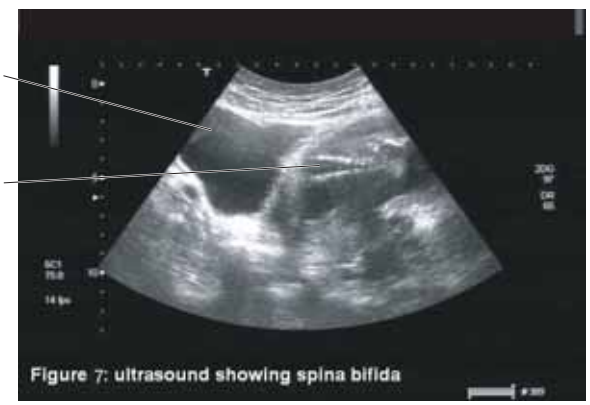


Figure 7: ultrasound showing spina bifida

The review reports the detection rate for encephalocele as 100%, although this is based on small numbers – 7 out of 7 cases across 11 studies[4].

Anencephaly can be detected by noting absence of the fetal skull and can be suspected as early as the 9th week. Spina bifida is diagnosed by looking for widening of the spine and assessing the skin overlying it. A banana shaped cerebellum and a lemon shaped fetal skull are also features.

CARIS data show that an abnormal ultrasound was detected in 412 of 436 mothers carrying a fetus with a neural tube defect. In 24 mothers the diagnosis was not made until delivery or miscarriage. This gives an overall case detection rate of 94.5 % Within this, detection rates for specific defects are as follows:

- Anencephaly 99.5% (184/185)
- Spina bifida 89.7% (183/204)
- Encephalocele 87.3% (48/55)

[4] Bricker L, et al. Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost effectiveness, and women's view. Health Technology Assessment. 2000; Vol 4: No 16

Neural Tube Defects

Alpha-fetoprotein

Serum alpha-fetoprotein is a protein mainly produced by the fetal liver. It enters the amniotic fluid through fetal urination and diffuses across the placenta into the maternal circulation.

Open neural tube defects (not covered by skin) cause alpha-fetoprotein to leak into the amniotic fluid and give a raised serum value.

Raised alpha-fetoprotein levels were reported in 100 cases of neural tube defect reported to CARIS. This represents about a quarter of all cases. Reporting of raised AFP levels to CARIS is not complete as this is no longer a screening test for neural tube defects in Wales. However, in practice, if a raised AFP is detected on routine Down screening it is likely to prompt an earlier antenatal anomaly scan.

Risk factors

In the majority of cases the cause of a neural tube defect is unknown. However some women are at increased risk of having a baby with the condition. The factors that can lead to this increased risk are:

- Mothers with a history of a previous pregnancy resulting in a fetus with a neural tube defect
- Mothers with type 1 diabetes mellitus
- Mothers with low serum folate levels

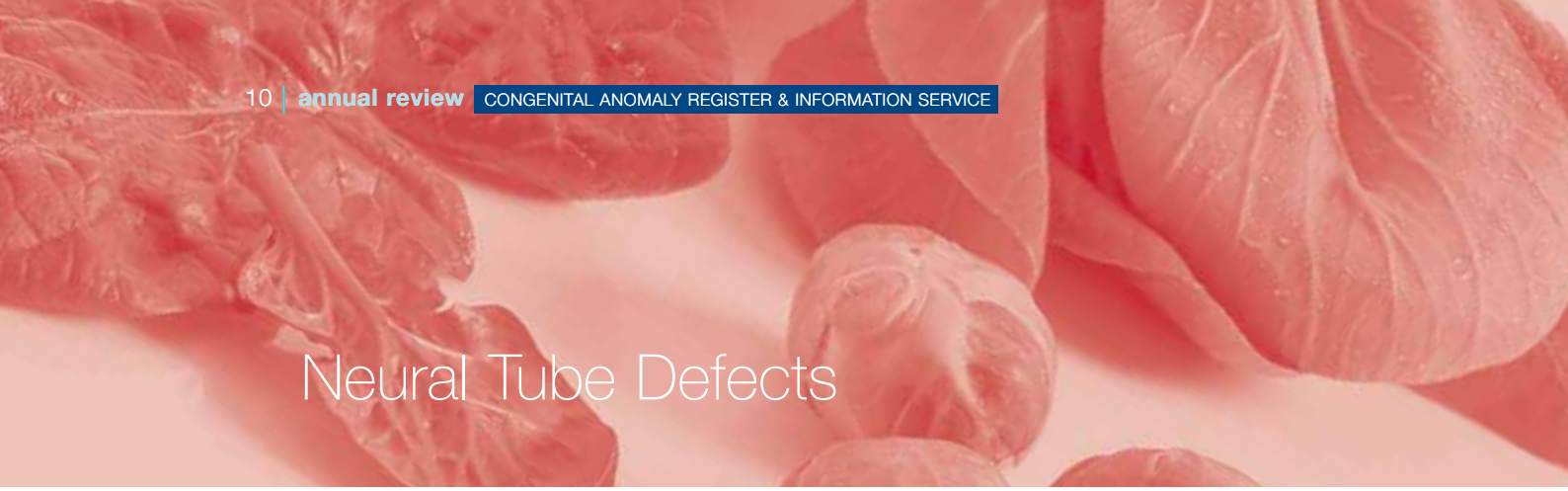
Low serum folate levels can arise because of:

- Low dietary intake of folic acid
- Taking certain epileptic drugs that can affect folate metabolism
- A genetic defect called methylene tetrahydrofolate reductase deficiency.

CARIS has the following data on these risk factors.

- Epilepsy was reported in 3.9% (13 / 331) mothers of babies with a neural tube defect where epilepsy status is recorded.
- Diabetes was reported in 4.7% (16 / 338) mothers of babies with a neural tube defect where diabetic status is recorded.
- 9 mothers were recorded as having had a fetus with a neural tube defect in previous pregnancies. This gives a recurrence risk of 2.1% in Wales (the lower end of quoted rates in the literature)[5]. It is likely that this figure will rise as CARIS collects further years of data.

[5] Harper, PS. Practical Genetic Counselling (5th Edn) 1998. Butterworth.



Neural Tube Defects

Folic Acid Campaign

The research evidence on folate supplementation suggests that it reduces the prevalence of neural tube defects substantially[6]. Guidance on periconceptual folic acid supplementation was first issued by the Department of Health in 1991. In 1992 the UK Expert Advisory Group went on to state that first occurrences of neural tube defects could be reduced by increasing folic acid consumption. Currently, folic acid supplements are recommended for all women prior to conception and during the first 12 weeks of pregnancy to help reduce the incidence of neural tube defects[5,7]. The recommended dose for women who are not at high risk of having a fetus affected by a neural tube defect is 400 mcgs daily.

It has been noted that although there was a decline in neural tube defect affected pregnancies between 1988 and 1999, there has been no detectable impact of the 1992 recommendation to increase folic acid intake[8]. There are a number of suggestions as to why this might be the case:[6-8]

- The high proportion of unplanned pregnancies limits the use of pre-conceptual supplements
- There is a slow spread of information to women of child bearing age and primary care providers about the importance of folic acid supplementation
- Women who know about the benefits of folic acid supplementation and who plan their pregnancies are not taking it at the right time

These findings have led to a debate about the fortification of flour as a public health measure, to increase the folic acid intake of all women of childbearing age. The Scientific Advisory Committee on Nutrition (SACN) has been considering this issue. In its report, Folic Acid and the Prevention of Disease (DOH 2005), it concluded that 'the universal fortification of flour with folic acid would significantly reduce the number of conceptions and births affected by neural tube defects'[8]. In June 2004 it was agreed not to introduce mandatory fortification at that time. This was due to concerns about vitamin B12 deficiency and in particular the risks to older people. There is concern that folate may mask signs of vitamin B12 deficiency[7].

SACN are reviewing the issue and have delayed the release of the latest report while they continue to evaluate increased folic acid intake.

[5] Harper, PS. Practical Genetic Counselling (5th Edn) 1998. Butterworth.

[6] Lumley J et al. Periconceptual supplementation with folate and / or multivitamins for preventing neural tube defects (Review) 2001. Accessed on line 2006 The Cochrane Collaboration. www.thecochranelibrary.com

[7] Abramsky L et al. Has advice on periconceptual folate supplementation reduced neural tube defects? The Lancet; 1999. Vol:354

[8] SACN. Draft report on folate and disease prevention. Nov 2005 www.sacn.gov.uk

Neural Tube Defects

figure 8: History of starting folic acid from 8244 mothers in Wales with pregnancy ending in congenital anomaly, 1998-2005.
Source: CARIS

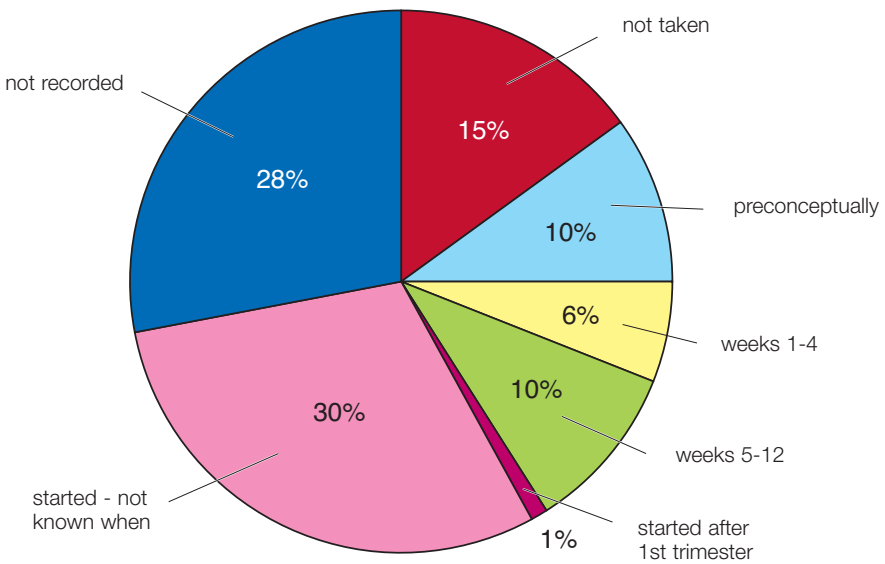


Figure 8 shows the pattern of folic acid supplementation in mothers reported to CARIS with a fetal abnormality and a fully completed CARIS form. There are limitations to the data as the recording of this information is not always consistent in the medical notes. The information was unrecorded or not found in 28% of case notes. In another 30% of case notes folic acid was recorded as taken but the start time was unrecorded. It can also be difficult for mothers to accurately recall their folic acid intake and the data in this can be subject to recall bias. Only 10% of mothers appear to take folic acid as recommended.

Our data also shows that around 15% of mothers never took folic acid. As might be expected some mothers who have not taken folic acid preconceptually start when they realise they are pregnant.

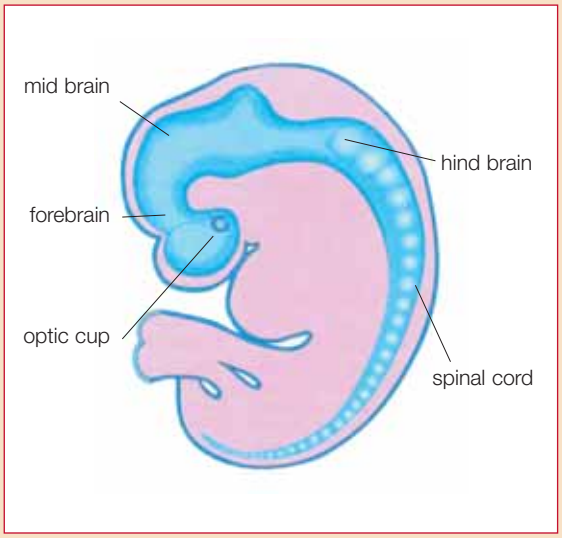
Of the 436 pregnancies affected by a neural tube defect, 200 mothers were reported as having taken folic acid supplements at some time during the pregnancy. 37 mothers reported taking it preconceptually. The proportions between neural tube defect mothers and all other mothers registered with CARIS are very similar for history of folic acid consumption.

Disorders of the Central Nervous System

Congenital anomalies of the central nervous system include disorders of the brain and spinal cord.

The basic structure of the brain and spinal cord develops in the first eight weeks following the last menstrual period. This is a complicated embryological pathway and as a result abnormal development of the brain is common (CARIS data shows a gross rate of 3.7 per 1000 live and stillbirths).

figure 9: central nervous system at 6 weeks gestation



Brain development[9]

Week 1 -	Last menstrual period.
Week 5 -	Neural plate forms from the primitive streak and curves to form the neural groove.
Week 6 -	Neural groove forms the neural tube with top two thirds becoming the brain and the lower third becoming the spinal cord. The top end closes first (failure to close can cause anencephaly or neural tube defect). Lumen of the tube forms the ventricular system and central canal. Substance of the tube forms the brain and cord. Forebrain, midbrain and hindbrain develop.
Week 7 -	Forebrain divides into two parts: i) cerebral hemispheres, caudate, putamen and lateral ventricles ii) thalami, hypothalamus, globus pallidus and third ventricle. Midbrain develops with formation of the aqueduct of Sylvius connecting the third and fourth ventricles. Hindbrain divides into two parts which contribute to the fourth ventricle: i) pons, cerebellar hemispheres and vermis ii) medulla (problems at this stage can cause holoprosencephaly and agenesis of the corpus callosum).
Weeks 9/10 -	Cerebral cortex forms as neurones migrate along fibres stretching from the lining of the ventricles to the brain surface.
Weeks 23/27 -	Development of gyri (ridges) and sulci (grooves).
Weeks 32/33 -	Development of secondary and tertiary sulci (problems at this stage can cause lissencephaly and schizencephaly).

[9] Before we are Born. Essentials of embryology and Birth Defects (6th Edn). Moore & Persaud. 2003 (Philadelphia) Saunders.

Disorders of the Central Nervous System

The early weeks of pregnancy represent the most vulnerable period of brain development but it continues to be suseptible to problems until delivery. Risks include sensitivity to medications particularly anti-convulsants, warfarin and anti-malarials, alcohol and recreational drugs. Environmental influences such as infection or irradiation can similarly affect development.

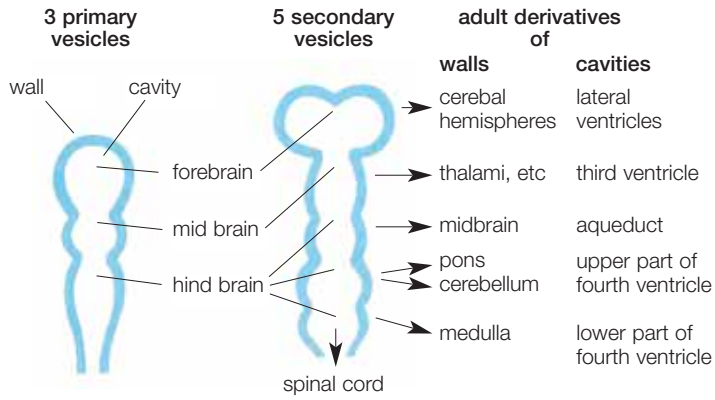


figure 10: fetal brain development

Congenital Anomalies of the Brain

Microcephaly

Though literally meaning small head, the term refers to restricted brain growth and often is associated with learning disability.

It can be present at birth or may develop in the first few years of life.

The baby's head fails to grow normally as it matures.

Antenatal diagnosis[10]

Microcephaly is suspected when the ultrasound measurement of head circumference lies below the 3rd centile for gestational age. The face appears of normal size.

It is important to exclude an underlying structural abnormality of the brain (neural tube defects, holoprosencephaly). Associated chromosomal disorders should be excluded.

Causes

a) Genetic causes – most chromosomal disorders, Angelman syndrome, Meckel- Gruber syndrome

b) Neurological disorders – von Recklinghausen disease, tuberous sclerosis

c) Environmental factors – cytomegalovirus, ionizing radiation, drugs including alcohol

Paediatric problems

Some children with microcephaly will have normal intelligence and a head that grows bigger but still remaining below the normal growth curves.

Common features in the baby:

- high pitched cry
- small head
- poor feeding
- seizures
- cerebral palsy
- developmental delay
- learning disability

[10] Textbook of Fetal Abnormalities. Twining P, McHugo J, Pilling D. 2000. Churchill Livingstone.

Disorders of the Central Nervous System

Microcephaly

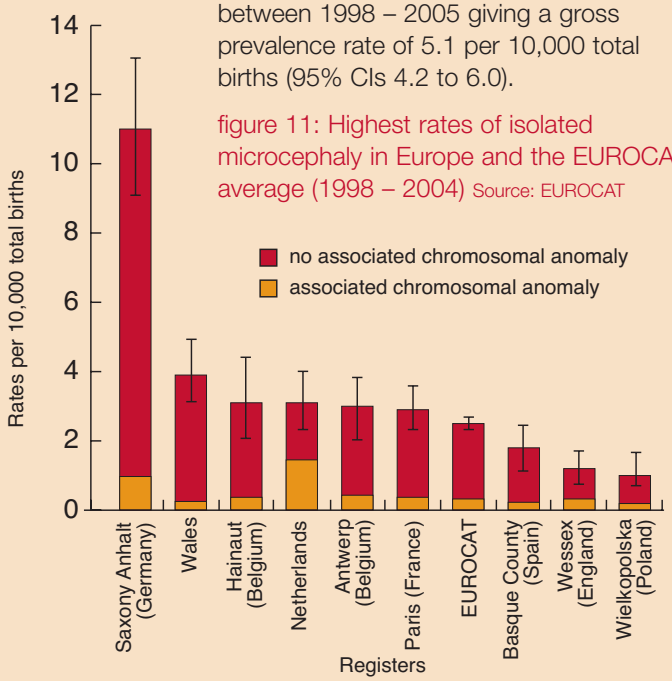
Outcome

No treatment exists to restore the baby's head to a normal size and shape. Support is required to maximise potential and cope with associated disabilities. Medication may help to manage fits, hyperactivity and neuromuscular symptoms.

Some infants will only have mild disability and the prognosis will vary with each individual.

130 cases have been reported to CARIS between 1998 – 2005 giving a gross prevalence rate of 5.1 per 10,000 total births (95% CIs 4.2 to 6.0).

figure 11: Highest rates of isolated microcephaly in Europe and the EUROCAT average (1998 – 2004) Source: EUROCAT



EUROCAT data shows particularly high rates of microcephaly in Saxony Anhalt (Germany). Wales rates are significantly higher than for EUROCAT as a whole but comparable to several other registers who have submitted data for a comparable period (figure 11).

Hydrocephalus

Hydrocephalus occurs when an abnormal amount of cerebrospinal fluid (CSF) accumulates in the ventricular system of the brain. The fluid can cause pressure in the brain and result in mental and physical problems.

It is the most frequent brain anomaly with a prevalence of around 1 per 1000 live births (CARIS data).

Causes

Hydrocephalus may occur as an isolated congenital anomaly[11] or may be associated with genetic conditions, intraventricular haemorrhage, maternal infections or neural tube defects.

When the condition is associated with chromosomal anomalies, outlook is poor with a high mortality and only half of the survivors developing normally.

For isolated hydrocephalus without associated anomalies, the outlook is much better.

The physical causes for the excess fluid include:

a) aqueduct stenosis – the canal connecting the 3rd and 4th ventricle becomes blocked meaning only the lateral and 3rd ventricles are dilated

b) posterior fossa obstruction (Dandy Walker syndrome, Arnold Chiari malformation related to neural tube defect)

c) choroid plexus adenoma - increased production of CSF

d) impaired resorption of CSF by arachnoid villi.

[11] Ouaba J et al. Prenatal isolated mild ventriculomegaly: outcome in 167 cases BJOG 2006; 113: 1072-1079

Disorders of the Central Nervous System

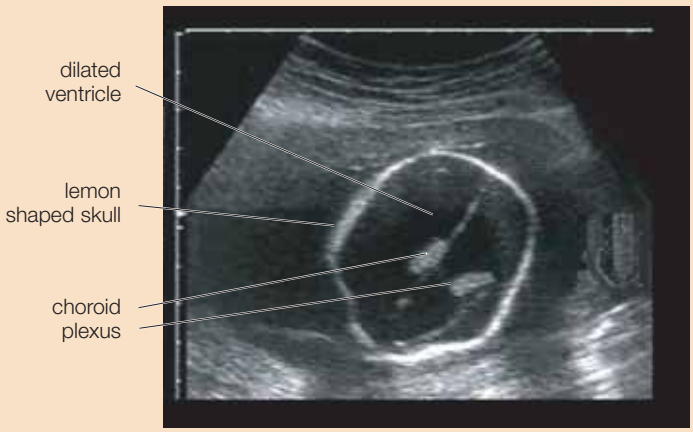


figure 12: ultrasound showing hydrocephalus

Antenatal diagnosis

This is possible in the second trimester. Measurements of the lateral ventricles greater than 10 mm indicate enlarged ventricles or ventriculomegaly. The choroid plexus can be seen as thinned or hanging down in the ventricle and may be an early sign of ventriculomegaly.

Isolated ventriculomegaly is considered mild when measuring between 10 and 15mm. There is a reported survival rate of 85%, with 85% of these children developing normally. Other anomalies should be sought and a fetal karyotype offered as the aneuploidy rate can be high.

Magnetic resonance[12] can be of value. Poor prognostic features include measurements greater than 12mm, progressive enlargement, asymmetrical ventriculomegaly and bilateral ventriculomegaly. Female sex also appears to adversely affect outcome. In most cases with no associated malformations, ventriculomegaly regresses or remains stable. Experience of antenatal ventriculo-amniotic shunting has not been encouraging.

Paediatric problems[13]

The accumulation of cerebrospinal fluid causes accelerated growth of the skull resulting in an increase in head circumference, widening of the fontanelles and sutures of the baby.

Symptoms

Headache or irritability
Vomiting
Anorexia
Drowsiness

Signs

Tense anterior fontanelle and splayed sutures
Scalp vein distension
Sunsetting (loss of upward gaze)
Neck retraction or rigidity
Pupillary changes
Neurogenic stridor
Decerebration – absence of cerebral function

[12] Whitby EH, Paley MNJ, Griffiths PD. Magnetic resonance imaging of the fetus. The Obstetrician & Gynaecologist 2006;8:71-77.
[13] Forfar & Arneil'sTextbook of Pediatrics. (5th Edn) Campbell & McIntosh. 1998. Churchill Livingstone.

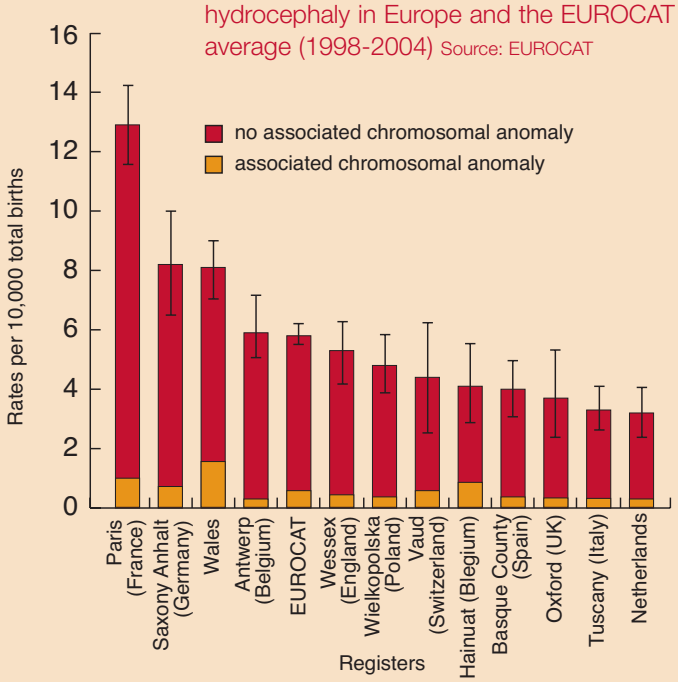
Disorders of the Central Nervous System

Outcome of hydrocephalus

Management depends on the cause of the hydrocephalus. The primary treatment involves positioning of a shunt draining the cerebrospinal fluid from the ventricles into the peritoneal cavity. This relieves the pressure on the brain and helps normal development.

CARIS has postnatal confirmation of 237 cases of hydrocephalus. This gives a gross prevalence of 9.3 per 10,000 total births (95% CIs 8.1 to 10.5). 150 cases were detected antenatally giving a detection rate of 63.3%.
Antenatal ventriculomegaly resolved spontaneously in 30 cases.

figure 13: Highest rates of isolated hydrocephaly in Europe and the EUROCAT average (1998-2004) Source: EUROCAT



Dandy Walker Syndrome

This results from a failure in the development of the cerebellar vermis resulting in:

– communication between 4th ventricle and cisterna magna

– a posterior fossa cyst

– cerebellar hypoplasia

Antenatal diagnosis by ultrasound and magnetic resonance

Associations

- chromosomal abnormalities (particularly trisomies) – 15-45%
- CNS associations
  - holoprosencephaly
  - agenesis of the corpus callosum
  - occipital encephalocoele
  - neuronal migration disorders
  - ventriculomegaly

Outlook – poor and depends on karyotype and other abnormalities

Dandy Walker Syndrome

55 cases have been reported to CARIS giving a gross prevalence of 2.2 per 10,000 total births (95% CIs 1.6 to 2.7). Of these, 14 were associated with chromosomal anomalies (26%).

Disorders of the Central Nervous System

Arnold Chiari Malformation

This is the commonest anomaly of the cerebellum involving:

- Descent of cerebellar vermis through foramen magnum into vertebral canal of upper cervical spine
- CSF absorption impaired resulting in hydrocephalus
- Banana sign of cerebellum on ultrasound
- Association with neural tube defect

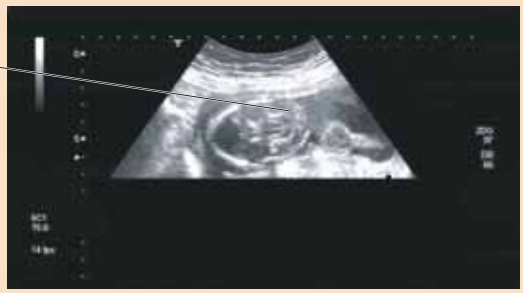


figure 14: ultrasound showing banana shaped cerebellum

Arnold Chiari Malformation

78 cases reported to CARIS giving a gross prevalence of 3.1 per 10,000 total births (95% CIs 2.4 to 3.7). 73 cases occurred as part of a neural tube defect (94%). 1 case was associated with Meckel-Gruber syndrome and the remaining 4 cases were isolated.

Holoprosencephaly

This results when the forebrain fails to divide into the lateral ventricles. Holoprosencephaly is a rare disorder (1 in 15,000 to 20,000 live births quoted). A recent study in the West Midlands reported 1 in about 6000 births and terminations with a higher prevalence in non-white ethnic groups. Though most affected infants die within 6 months some can survive infancy (5 out of 16 livebirths in this study)[14]. CARIS data include 36 cases, giving a gross prevalence of 1.4 per 10,000 total births (95% CIs 0.9 to 1.9) or 1:7090 cases - a similar finding to that of the West Midlands register.

Defects in forebrain development usually also include facial abnormalities. There is a strong association with major abnormalities, trisomy 13 and other chromosomal problems.

It is thought that this severe spectrum of anomalies stems from genetic or environmental problems occurring as early as the fifth to the seventh week of development. There is an association with maternal diabetes.

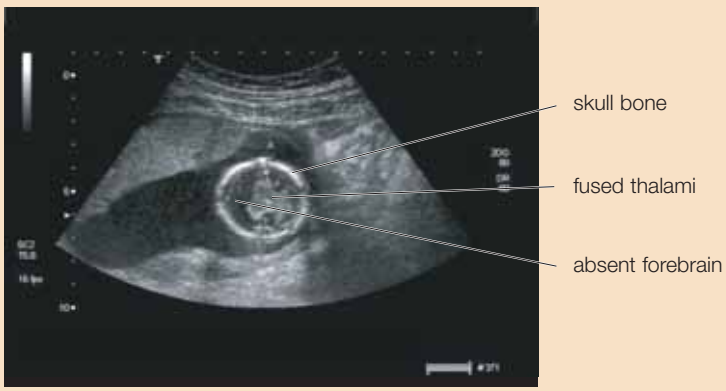


figure 15: ultrasound showing holosencephaly

Antenatal diagnosis

This is usually diagnosed in the second trimester. Fused thalami can be seen protruding into the large single ventricle. There is microcephaly and brachycephaly (when the biparietal diameter is large compared to the head circumference). The cavum septum pellucidum is absent and the cerebral mantle is incomplete.

[14] Ong S et al. An epidemiological study of holoprosencephaly from a regional congenital anomaly register: 1995 – 2004. (in press)

Disorders of the Central Nervous System

Holoprosencephaly

Outcome

Because of the severity of the defect the prognosis is poor. Termination of pregnancy is usually offered.

Genetic counselling for future pregnancies is essential, with a quoted recurrence risk of 6% in those where there was no chromosomal abnormality.

Among CARIS cases, 6 were liveborn, of which 2 died within the first year of life. This gives a survival prevalence at 1 year of life of 11% of recorded cases or 0.2 per 10,000 total births .

2 fetal losses and 1 stillbirth were reported. In the remaining 27 cases, pregnancy was terminated.

17 cases had chromosomal abnormalities of which 12 were Trisomy 13.

Just one mother was known to have insulin dependent diabetes.

Lissencephaly and Schizencephaly

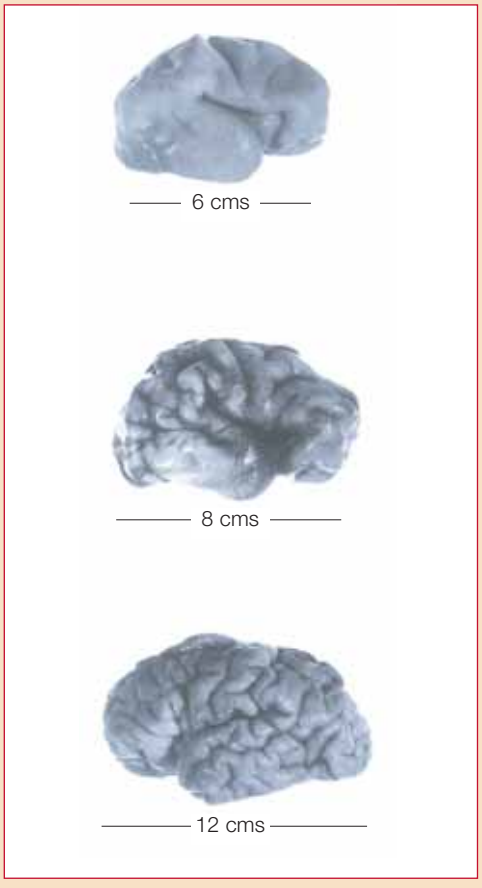
The surface of the brain hemispheres is initially smooth. As growth occurs sulci (grooves) and gyri (convolutions) develop. These both allow a large increase in the surface area of the cerebral cortex without greatly expanding the size of the cranium.

Lissencephaly (smooth brain)

In this condition, the brain fails to develop normal gyri and sulci that are features of a mature brain. In normal development, the brain surface is featureless until the lateral sulcus develops during the fifth month. The brain then becomes increasingly folded with fissures and sulci from 28 weeks. As the brain surface may not begin to look like the adult appearance until as late as 36 weeks gestation, this condition is rarely diagnosed antenatally. Magnetic resonance imaging has been reported as being useful diagnostically.

There is an association with disorders of neuronal migration, midline development and several syndromes including agenesis of the corpus callosum. Abnormalities of chromosome 17 can be present.

figure 16: development of cortigal gyral patterns



Disorders of the Central Nervous System

With such pathology the prognosis is poor with learning problems and developmental delay.

17 cases of this defect have been reported to CARIS giving a gross prevalence of 0.7 per 10,000 total births. A microdeletion from chromosome 17 (Miller-Dieker syndrome) was associated with 1 case.

Polymicrogyria forms part of the same spectrum of brain anomaly and 4 cases have been reported to CARIS (a gross prevalence rate of 0.2 per 10,000 total births).

Schizencephaly (split brain)

This occurs when there is a complete cleft through the cerebral hemisphere. This means that there is a communication between the ventricular system and the subarachnoid space. The clefts are usually in the parietal lobe, may be unilateral, and are often asymmetric.

Schizencephaly is thought to be related to a disorder of blood supply and cocaine has been implicated in its development.

Again magnetic resonance imaging (MRI) offers the best chance of diagnosing the condition.

The outlook ranges from seizure management alone to dealing with hemiparesis, global development delay and motor problems.

Just 3 cases have been reported to CARIS giving a gross prevalence of 0.1 per 10,000 total births.

Agenesis of the Corpus Callosum

The corpus callosum connects the two cerebral hemispheres across the midline. Its fibres are fully formed by the 20th week of gestation.

Diagnosis

- Antenatal ultrasound – mild ventriculomegaly, absent cavum septum pellucidum
- MRI can be helpful in making a diagnosis

Associations

- Other CNS disorders, genetic syndromes, inborn errors of metabolism, and aneuploidy (trisomies 8,13,18)

Outlook

- Isolated agenesis has 85% chance of normality

Agenesis of the Corpus Callosum

43 cases have been reported of either total or partial agenesis. This gives a gross prevalence rate of 1.7 per 10,000 total births (95% CIs 1.2 to 2.2).

12 cases were associated with chromosomal anomalies, including 5 cases of Trisomy 18 and 2 cases of Trisomy 13. Two cases had teratogenic causes (1 fetal alcohol syndrome & 1 warfarin embryopathy).

Intrauterine Infection and the Fetal Brain

Infection affecting the fetal brain can cause haemorrhage, cerebral necrosis from ischaemia, calcification or ventriculomegaly.

Infection can also cause anaemia and thrombocytopenia which result in the most common problem, an intracranial bleed. This can occur into the ventricles and cause hydrocephalus or bleed into the brain substance forming a porencephalic cyst (lined with white matter and filled with CSF).

Disorders of the Central Nervous System

Infection early in the pregnancy may affect neuronal migration and cause lissencephaly.

Microcephaly can be seen in infection with cytomegalovirus, rubella, toxoplasmosis, varicella, human immunodeficiency virus (HIV).

Hydrocephaly can be seen in infection with CMV, herpes simplex, treponema pallidum and varicella.

CARIS has some data on congenital infections, especially where associated anomalies are suspected (*table 3*). It is likely however, that many cases go unnoticed or unreported.

Table 3: All congenital infections reported

Source: CARIS

Congenital Infection	number
Parvovirus	14
Cytomegalovirus	12
Hepatitis (B & C)	10
Total viral infections	40
Congenital pneumonia	44
Toxoplasmosis	6

Diastematomyelia

Diastematomyelia involves tethering of the spinal cord caused by a bony or cartilaginous spur of the vertebral column. The cord is divided around the spur and usually reunites below it.

Embryologically it derives from persistence of the neuroenteric canal which then splits the cord.

Maternal diabetes has been reported to be linked to the condition.

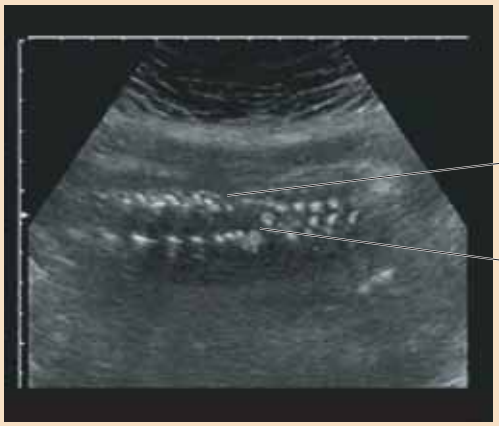


figure 17: ultrasound showing diastomatomyelia

There is a strong association with neural tube defects (36%). Kyphoscoliosis and skin changes above the area are common.

Antenatal diagnosis

On ultrasound, widening of the posterior ossification centres can be seen together with the presence of a central focus representing the spur.

Magnetic resonance offers further definition of the spinal cord especially if there is associated spina bifida.

Outcome

It is important to exclude spina bifida if diastematomyelia is discovered antenatally.

Babies born with this may be entirely normal or have neurological problems as severe as spastic paraplegia.

Early surgery to remove the bony spur can prevent progressive tethering of the cord as the baby grows.

Only 5 cases have been reported to CARIS giving a gross prevalence of 0.2 per 10,000 total births. 2 cases are associated with known syndromes (1 VATER association and 1 caudal dysplasia sequence).