Antenatal counselling for prospective parents whose fetus has a neurological anomaly: part 2, risks of adverse outcome in common anomalies

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Antenatal counselling for families whose fetus has neurological anomalies: Part two – risks of adverse outcome in common abnormalities

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WHAT THIS PAPER ADDS

- Isolated VM<15mm is associated with atypical development in 7-8% and in 30-40% of isolated VM>15mm where VP shunt insertion rates are 20-30%. Larger degree of VM and progressive increases are associated with worse outcomes.
- Isolated agenesis of the corpus callosum is associated with normal outcome in 76% and severely atypical developmental outcomes in 8%.
- Isolated microcephaly 2-3 SD below the mean is likely to be associated with normal outcome and >3SD below the mean likely to have atypical developmental outcome. Isolated macrocephaly is likely to be associated with normal outcome.
- HPE is strongly associated with chromosomal and genetic abnormalities, perinatal death or atypical developmental outcome. Outcomes in other cerebral / cortical malformations are dependent on the extent of the lesion, regions of the brain affected, presence of other abnormalities and aetiology.
- The outcome data on posterior fossa abnormalities is lacking. DWC is associated with developmental difficulties in up to 60% of fetuses, whilst the Blake Pouch cyst gives a similar risk to the general population. A small cerebellum in early gestation may exhibit catch-up growth.
- Counselling of MMC should involve a multidisciplinary team with knowledge of the all long-term outcomes and should not be incorrectly catastrophic. Fetal surgery should be discussed, where appropriate.

ABSTRACT

Following diagnosis of a fetal neurological abnormality, prospective parents want to know the best and worst-case scenarios and an estimation of the risk for their fetus having atypical developmental outcome. The literature on developmental outcomes for fetal neurological abnormalities is poor: studies are characterised by retrospective design, small sample size, often no standardised assessment of development, and differing definitions of abnormality. This paper provides an aide-memoir on the risks of adverse neurodevelopmental outcome for ventriculomegaly, cortical abnormalities, microcephaly, macrocephaly, agenesis of the corpus callosum, posterior fossa abnormalities, and myelomeningocele to assist health care professionals in counselling. The data in this paper should be used alongside recommendations on counselling and service design in paper one to provide antenatal counselling.

INTRODUCTION

Once a fetal neurological anomaly has been diagnosed by ultrasound or in-utero magnetic resonance imaging (iuMRI), prospective parents want to understand the aetiology and likely developmental outcome. Part one of our review discussed prospective parents' views on antenatal counselling and recommendations for how services should be designed and risks communicated.[1] To ensure prospective parents receive appropriate advice and support, a multidisciplinary team (MDT) should be involved in the diagnosis and discussion of likely outcome. The most appropriate professionals should then provide counselling in easy-to-understand language, discussing management options for the pregnancy, as well as postnatal interventions and follow-up. Support should also be available from psychologists and social workers.

Part two of our review provides pragmatic information on aetiologies and risks of atypical developmental outcome for common brain anomalies in the fetus. Although we discussed in part one that fractions, with similar denominators, are better for comparing risk than percentages, we use percentages for clarity here.

PREPARATION FOR COUNSELLING

Before starting counselling, health care professionals should collect as much information as they can from a range of sources, including the prospective parents, including:

- any family history of developmental problems, miscarriages, or deaths in early childhood
- additional fetal abnormalities
- whether the abnormality has changed over time
- fetal growth pattern
- head size and shape
- results of congenital infection screen

results of genetic testing.

For most indications, karyotype analysis has been superceded by chromosomal microarray, which detects an additional 4-10% copy number changes (microdeletions and microduplications) in fetuses,[2-8] but does not detect balanced rearrangements. More recently, next generation sequencing has become more available in prenatal care, which has allowed large numbers of genes to be sequenced in parallel. For some indications with a relatively defined phenotype, gene panels can be interrogated, but for less well defined phenotypes or those that may have diverse aetiologies, whole exome or whole genome analysis can be undertaken.[9] The PAGE study found whole exome sequencing revealed an aetiology in 8.5% of fetal anatomical abnormalities where karyotype and microarray were normal, and 15.4% in multi-system involvement, with multiple anomalies and those affecting the heart and skeletal system having the highest yield.[10] Other studies have found exome studies to be similarly useful,[11; 12] depending on cohort size, inclusion criteria, family cases, and consanguinity. A recent meta-analysis suggests a weighted average for diagnostic rate of 19%, with the data too limited for nervous system abnormalities.[7] The rates of genetic abnormalities of unknown significance are around 9-20% for all fetal anomalies.[7; 12; 13] Health economic analysis suggests it is more cost-effective to perform exome sequencing after microarray, rather than abandon chromosomal studies altogether.[14] The data on prenatal genome studies is more limited, but it may detect more pathogenic abnormalities than exome sequencing.[15; 16]

There are a number of challenges presented by exome sequencing: there is less phenotypic information available in the fetus compared to a child to decipher the significance of genetic abnormalities; databases for fetuses are not well established; there is no agreement on whether to report variants of unknown significance; phenotypic variation in single gene disorders can make prognostication difficult; and unrelated abnormalities of clinical significance may be found.[6; 7; 17; 18] Health care professionals should be aware of the stress

caused by an abnormal fetal exome result,[19] and ensure appropriate genetic counselling and psychological support is available. In reality, not all of this information may be available at the time of counselling. Counselling should then take a stepwise approach, with further discussions held as more information is obtained.

It is important to consider the baseline population rate of developmental problems: 10% of children have developmental difficulties, including specific learning difficulties, attention problems, autistic spectrum disorders, and developmental coordination disorder;[20] 2-3% have early developmental impairment (EDI), defined as developmental skills >2 standard deviations (SD) below the population mean in 2 or more developmental domains.[20] The problems with fetal outcome studies are that most are retrospective, at high-risk of selection bias, only provide short-term outcome data, and do not use standardised developmental assessments. Existing studies may involve health care professionals, who have not received training in child development, telephoning families to ask how their child is. Where standardised tests are used, different definitions of atypical development and descriptive terms are used; for example, a child with a developmental ability in the low normal range may be described as mildly, moderately, or severely "abnormal" in different studies. Data on rates of "adverse outcome" may also include terminations of pregnancies, stillbirth and/or perinatal deaths. Therefore, health care professionals should be cautious about what figures they use.

VENTRICULOMEGALY

Fetal ventriculomegaly (VM) is defined as the ventricles being larger than 10mm at the level of the atria, i.e. 3-4SD above the population mean. It can be sub-classified as:

- Mild 10-15mm, severe ≥15mm, or
- Mild 10-12mm, moderate 13-15mm, severe ≥15mm.
- Borderline 10-12mm, mild 13-15mm.

These terms ignore important information, such as aetiology, presence or absence of other abnormalities, and whether ventricular size changes as the pregnancy progresses.

Ventriculomegaly occurs because of a range of processes:

1) a normal variant
2) cerebral atrophy from degenerative abnormalities (e.g. metabolic disease, congenital infection, infarction, single gene disorders)
3) obstruction to cerebrospinal fluid (CSF) flow, such as aqueductal stenosis, Arnold Chiari malformations, intracranial haemorrhage, congenital infection
4) impaired absorption of CSF, such as following intracranial haemorrhage or congenital infection
5) increased CSF production from choroid plexus papilloma
6) other causes, including single gene or chromosomal abnormalities, structural abnormalities affecting the shape of the brain and ventricles.

The results of large cohort studies of fetuses with VM are shown in table 1, and a flow chart to aid counselling in figure 1.

Ventriculomegaly measuring <15mm

The risk of adverse developmental outcome with fetal VM 10-15mm and additional abnormalities depends on the nature of the abnormalities, so pooled prevalence figures are of limited value: health care professionals should use their experience to determine the significance of these findings. There is more outcome data for isolated fetal ventriculomegaly. The definitions and inclusion criteria for "isolated VM" (iVM) vary between studies, and include:

- absence of other central nervous system (CNS) abnormalities
- absence of abnormalities in other CNS structures and body systems
- absence of other abnormalities and normal fetal karyotype and congenital infection screen, with exclusion of women who declined amniocentesis for karyotype

- absence of other abnormalities and normal karyotype and congenital infection screen, with inclusion of women who declined karyotype.

A meta-analysis of 1213 fetuses with iVM found abnormal karyotypes in 4.7%, and atypical developmental outcome in 7.6% at a mean age of 27 months.[21]. More recent studies agree with this figure.[22-25] Developmental outcome is similar in iVM 12-15mm compared to 10-12mm,[22-24; 26], and our view is the term "moderate VM" can cause unnecessary anxiety and should be abandoned. Unilateral VM (one ventricle is >10mm and ≥2mm difference between the size of the lateral ventricles) and asymmetrical VM (both lateral ventricles >10mm, but least a 2mm difference between sides) have similar outcomes to bilateral VM.[27-31]

Based on this evidence, it is worth questioning whether isolated VM 10-15mm increases the risk of early developmental impairment. Our answer is "probably not". The baseline risk of EDI is 2-3%, but few studies use this strict definition and include children with milder developmental abnormalities.[22; 23; 32-35] When comparing the published data in isolated VM 10-15mm to the 10% general population prevalence of developmental difficulties, the figures are equivalent.

Ventriculomegaly measuring >15mm

A meta-analysis of outcomes of 110 fetuses with iVM >15mm showed the pooled proportion of stillbirth or perinatal death was 12.1%. Of the surviving babies, developmental outcome was normal in 42.4%, mild/moderate abnormal outcomes in 18-30% (defined as developmental scores 1-2SD below the mean), and severely abnormal in 30-40%.[22; 36] The rates of ventriculo-peritoneal shunt insertion (VPS) were 21.4-29.5%.[26; 37] Larger and progressive ventriculomegaly are the most likely to require neurosurgical intervention and usually have adverse developmental outcome.[31]

Key points: Isolated VM <15mm is associated with developmental difficulties in around 7-8% cases, which is either the same or slightly higher than the general population. VM >15mm is associated with a "severely atypical developmental outcome" in 30-40%, and the rate of VP shunt insertion is 20-30%. Larger degree of VM, progressive increases in ventricular size, and additional abnormalities are associated with worse outcomes.

AGENESIS OF THE CORPUS CALLOSUM (ACC)

Abnormalities of the corpus callosum (CC) are "isolated" in 50% of cases and associated with other abnormalities in the other 50%.[38] Repeated MRI in the third trimester may detect subtle additional abnormalities invisible on earlier imaging. ACC may be complete or partial. Hypoplasia, where CC has formed but is thin, may also be included in follow-up studies. The relative proportions of these subgroups are similar between isolated and non-isolated ACC groups: 55-60% are complete ACC, 15-25% partial, 12-15% hypoplastic.[38] Chromosomal abnormalities are seen in between 5-10% of ACC on microarray.[39] The definition and significance of a short corpus callosum is unclear.

The ranges of aetiologies and developmental outcomes in ACC are vast, ranging from normality to stillbirth, perinatal death, or profound developmental disabilities. It is difficult to give an accurate prognosis for any individual fetus unless the aetiology is known to have a poor prognosis. The main outcome studies into ACC are summarised in table 2 and figure 2. A meta-analysis of 53 fetuses with isolated complete ACC showed normal developmental outcome in 76%, borderline/moderate difficulties in 16%, severe developmental abnormalities in 8%; 7% had epilepsy. The rates of developmental difficulties with partial ACC were similar.[39] Data on ACC and other associated abnormalities is limited, with atypical developmental outcome noted in 75% of 8 infants.[40]

Most of the studies included do not assess outcome beyond childhood: subtle cognitive difficulties, including difficulties with attention, and other executive functions, are known to

occur in ACC.[41-43] The prevalence of ASD in ACC is unknown, but studies of community diagnoses of ACC have suggested rates of 45% in children, 35% adolescents, and 18% adults on screening questionnaires.[44] These is likely to be an over-estimate. Studies comparing children with ACC to those with ASD and normal corpus callosum, suggest children with ACC have milder autistic traits, which are typically seen after age 6 years, and less attentional, anxiety, depressive symptoms, social difficulties, unusual thoughts, and repetitive / restrictive behaviours than children with ASD.[45] Prospective parents should be advised to seek medical and psychological assessment if they become concerned about their child's academic progress and behaviour at school age. It is also recommended that postnatal developmental follow-up is offered, preferably until at least school age, to allow for early diagnosis and support.

Key points: around 50% of fetuses with ACC are associated with other abnormalities, and 50% are isolated. In isolated cases, normal outcome is seen in around 76% of cases and severely atypical developmental outcomes in 8%. Subtle cognitive difficulties and autistic traits may not become apparent until school age.

MICRO- AND MACROCEPHALY

There is disagreement on the definition for microcephaly, with both >2 and >3SD below the population mean for the occipito-frontal diameter proposed. An unusual head shape can yield a small head circumference, which is why biparietal diameters should not be used on their own to diagnose microcephaly. Unusual head shapes in the vertical plane, such as in craniosynostosis, can be excluded using the foramen magnum-to-cranium distance (FCD).[46] Whatever values are used, over-diagnosis of fetal microcephaly remains a significant problem.[47-49] The rate of head growth is also important, with head circumference (HC) falling off the centiles being more significant than a small head tracking along a lower centile,[50] so repeated imaging is important.

In paediatrics, the definition of >3SD below the mean HC is recommended because outcomes are usually normal and genetic diagnoses rare between 2-3SD below the mean.[50] This is consistent with a single study of 19 fetuses whose HC were 2-3SD below the mean, all of whom had normal outcomes, although behavioural problems were common.[48].

For "isolated" cases >3SD below the mean, and those falling off the centiles, there is no high-quality data to estimate the risk of adverse outcome, but it is likely to be high. Health care professionals can struggle to find published figures on how many SD a fetus' HC lies below the mean, so we have generated these values in table 3 from Chitty et al's data,[51] which is used routinely in the UK. Other published values exist, including recent data from the Intergrowth-21st study.[52; 53] Population specific values should be used. Where other structural, genetic, or infective abnormalities are found, clinicians need to tailor their prognostication to the nature of these findings.

Macrocephaly is diagnosed when the fetal HC is either 2SD above the population mean for gestational age or above the 95th centile and is differentiated from hydrocephalus by ventricular size. Most cases are familial in origin, and it is worth measuring and plotting the biological parents' HCs to determine if their head sizes are large. Reported developmental outcomes from small studies are usually normal in isolated cases.[54-56]

Where there are other malformations, possible aetiologies include Sotos syndrome (NSD1 gene), mutations in the NFIX gene, Neurofibromatosis type 1 (NF1), Klippel-Trenaunay Syndrome, conditions associated with capillary malformations, including the macrocephaly-capillary-malformation syndrome, and Cowden syndrome, which is associated with hamartomas and mutations in the PTEN gene.[57; 58] Other aetiologies include fetal tumours, expanding intracranial cysts, megalencephaly, and Glutaric Aciduria Type 1. Therefore, a detailed search should occur for other abnormalities, including limb overgrowth, abnormal

shape to the Sylvian fissures, polydactyly, cardiac and kidney abnormalities, ascites, and facial anomalies.

Key points: isolated microcephaly 2-3 SD below the mean is likely to be associated with normal outcome. Microcephaly >3SD below the mean, when associated with other abnormalities, and where the fetal head circumference is progressively falling away from the centiles, are likely to have atypical developmental outcome. Isolated macrocephaly is likely to be associated with normal outcome.

HOLOPROSENCEPHALY (HPE)

Holoprosencephaly is a failure of forebrain division into the two cerebral hemispheres, deep grey matter (basal ganglia and thalami), olfactory and optic bulbs and nerves. It is a spectrum of abnormalities:

- Alobar HPE, the most common and severe form, with no separation of the cerebral hemispheres or formation of the CC; a single large ventricle; cyclopia, hypotelorism, anopthalmia, or microopthalmia; proboscis; and cleft lip and palate
- Semilobar holosprosencephaly involves fusion of the frontal and parietal lobes with likely abnormal facial features.
- Lobar holoprosencephaly involves fusion of only the frontal lobes, sometimes with involvement of the deep grey matter, and may or may not be associated with closely spaced eyes, depressed nasal ridge, and cleft lip and palate.[59-63]
- Mild interhemispheric variant (syntelencephaly) where the posterior frontal and parietal lobes fail to separate, with or without fusion of the deep grey matter, and absence of the body of the CC.[64; 65]

Chromosomal abnormalities are seen in 24-54% of HPE, typically trisomy 13,[59; 62; 66], and at least 10% will have microdeletions or microduplications on microarray,[66; 67]; 19-25% have a

single gene disorder, with autosomal dominant, autosomal recessive, and X-linked inheritance patterns described.[66] Alobar HPE has traditionally been associated with stillbirth or death in the neonatal period. Health care professionals should avoid counselling families that "all" babies die shortly after birth because a proportion do not: 50% of babies with alobar HPE and a relatively normal face die within 5 months of age, 20-30% live at least a year, and survival to 11 years is described.[59; 61] In semi-lobar HPE, one study found 2/11 (18.2%) died in the first week, 3 (27.3%) died by 6 months, 5 (45.5%) by 3 years, and 4 (36.3%) were alive beyond 4 years of age.[59] Survival into adulthood is known.[61]

Children with HPE have developmental difficulties.[59; 61; 63] Children with alobar holoprosencephaly do not sit, mobilise, reach for objects, or speak, and may have mild hypotonia or spasticity.[61] 56% require treatment for epilepsy.[63] They may be able to hear and react to noises and, if they have eyes, may fix, follow, and recognise familiar faces. Other difficulties include feeding problems, drooling, gastrointestinal reflux disease, aspiration, respiratory tract infections, abnormal high-pitched crying, behavioural and sleep problems, irregular breathing, heart rate, and temperature control.[61; 63] Children with semi-lobar HPE may have profound learning difficulties, but some children will walk a few assisted steps, have comprehension of single word phrases, and a small repertoire of single spoken words.[60; 63] In lobar HPE, 50% of children walk, hand function may be mildly impaired, and children may speak in single word or short phrases.[60; 63] The middle interhemispheric variant of HPE have outcomes similar to lobar HPE.[64]

Children with HPE are at risk of diabetes insipidus and other endocrinopathies.[59; 61; 63] Hydrocephalus may present, especially in alobar and semilobar HPE associated with a dorsal cyst, and 16% require a VPS.[63]

Key points: HPE is strongly associated with chromosomal and genetic abnormalities, particularly trisomy 13. Fetuses with facial abnormalities are more likely to die in the

perinatal period or have more severe developmental difficulties, but even those with a normal face are likely to have atypical developmental outcomes.

MALFORMATIONS OF CORTICAL DEVELOPMENT

The brain has few sulci and gyri in early gestation, and these develop in an organised manner in the second and third trimester. The introduction of in-utero MRI (iuMRI) means that identification of cortical and migration abnormalities is better, but false positives and negatives still occur. Repeated iuMRI in the third trimester may be needed identify subtle abnormalities.[68; 69] Abnormalities include hemimegalencephaly, lissencephaly, cobblestone malformation, polymicrogyria, and heterotopia.

Hemimegalencephaly, which may also be associated with brainstem and cerebellum anomalies,[70] often results from single gene disorders, including mutations in the PI3K-ATK-MTOR pathways and associated tuberous sclerosis complex, NF1, Sturge Weber, Klippel-Trenaunay Syndrome, and other neurocutaneous disorders.[71; 72] Developmental outcome is poor, with motor difficulties including cerebral palsy, learning difficulties, and refractory epilepsy, although early hemispherectomy may benefit 50-60%.[73-75]

Lissencephaly, in which neuronal migration is impaired and either an absence (agyria) or reduction (pachygyria) in gyral formation results, can be an isolated finding or associated with other features. Many genes can be associated with lissencephaly.[76] The commonest are PAFAH1B1 (OMIM 607432) and DCX (OMIM 300067, also associated with ACC), both of which may also be associated with subcortical band heterotopia. Other genes include ARX (OMIM 300215) and TUBA1A (OMIM 611603). Miller-Dieker syndrome (OMIM 247200) should be considered where there is facial dysmorphia, a prominent forehead, midface hypoplasia, small nose and jaw, low set ears, renal or cardiac abnormalities, or omphalocele. The presence of cerebellar dysgenesis, basal ganglia dysmorphia, and

brainstem abnormalities raises the possibility of tubulinopathies, whilst cerebellar hypoplasia suggests CDK5 (OMIM 616342) and RELN mutations (OMIM 257320).[76] Where intracranial calcification, white matter hyperintensity, or temporal lobe cysts are seen, congenital CMV is likely.[77] Whatever the cause, the likelihood of developmental difficulties and epilepsy will be high, and dependent on the degree of cortical abnormality.

Cobblestone malformation, in which sulcation is preserved but the cortex is "bumpy", is associated with congenital muscular dystrophies, including dystroglycanopathies like FKTN (OMIM 253800), B3GALNT2 (OMIM 615181), FKRP (OMIM 613152), POMT1 (OMIM 236670), and POMT2 (OMIM 613150) mutations. These are associated with eye abnormalities, contractures, ventriculomegaly, cerebellar hemisphere and vermis hypoplasia or cysts, kinked brainstem, or a bifid pons.[78] Neonates with these conditions usually die within the first year or have a range of developmental difficulties, including epilepsy, weakness, poor respiratory function, feeding problems, and contractures, all of which will require multidisciplinary care.[79; 80]

Polymicrogyria can be focal, multifocal, or diffuse and can affect one or both hemispheres. The aetiology can be primary genetic or a result of an insult occurring between 16 and 24 weeks gestation, such as congenital CMV and Fetal Alcohol Syndrome.[81] There is a wide range of genetic causes,[82] including metabolic conditions like peroxisomal disorders.[83] Tubulinopathies, as with all the other forms of cortical malformation, are a potential cause, and may include dysmorphic basal ganglia.[84] Outcome will be dependent on the aetiology and extent of the cortical abnormality.

Heterotopia can be nodular in the periventricular region, subcortical or band-like. Periventricular nodular heterotopia may be isolated or diffuse, and can be associated with other abnormalities, such as ACC, cerebellar, or brainstem abnormalities. Although genetic aetiologies are known, it is unusual to find an aetiology antenatally, and there should be a

careful search for other structural abnormalities in the fetus, including signs of tuberous sclerosis.[80] Outcome may be normal for cases of isolated nodular heterotopia, and our experience is that incidental isolated heterotopia can be found in well older children and adults undergoing neuroimaging for other reasons. With increasing number and severity of heterotopia, the risk and severity of developmental difficulties increases, but there is little high-quality data to help delineate outcome in more detail.

Key points: cortical malformations have a wide variety of causes, severity and outcomes. Outcome is dependent on the extent of the lesion, regions of the brain affected, presence of other abnormalities and, if found, aetiology.

POSTERIOR FOSSA ABNORMALITIES

Cerebellar agenesis, hypoplasia, or atrophy

It can be hard to differentiate cerebellar hypoplasia and atrophy, unless there is evidence of a normal cerebellum early in pregnancy.[85] Potential causes include:

- chromosomal abnormalities, with one study finding 6/11 (54.6%) fetuses with cerebellar hypoplasia having a significant abnormality on microarray (33.3% for isolated and 88.9% for additional abnormalities)[86]
- single gene disorders, such as ciliopathies, dystroglycanopathies, tubulinopathies
- syndromic causes, including PHACES association (posterior fossa abnormalities, haemangioma, arterial lesions, cardiac abnormalities, eye problems, and sternal notch or dimple)
- metabolic disorders, including carbohydrate deficient glycoprotein disorders
- fetal exposure to toxins like fetal alcohol syndrome
- congenital infection, especially CMV
- haemorrhage.[87]

Fetuses with isolated cerebellar hypoplasia or atrophy are at high risk of developmental difficulties,[88] but there are few follow-up studies to provide figures. A review of children with pre and postnatally diagnosed cerebellar disorders noted that bilateral cerebellar hypoplasia was associated with cognitive/developmental impairment in 60-100% of cases, language difficulties in 44-89%, and behavioural problems were also common.[89] To complicate matters, we have also seen fetuses with small cerebellums at 20-22 weeks, where growth has continued throughout pregnancies and the cerebellum has appeared normal in the third trimester.

Unilateral hypoplasia or atrophy is postulated to be related to cerebellar haemorrhage. The range of potential outcomes is broad: Poretti et al studied 7 children and found 2 had normal outcome apart from minimal ataxia, 3 had mild learning disabilities, and 2 children with cognitive abilities in the normal range had either expressive language difficulties or ataxia. None had severe or profound learning disabilities or motor deficits.[90] A review of children with pre and postnatally diagnosed cerebellar disorders noted that unilateral cerebellar hypoplasia was associated with cognitive impairment in 17-50% of cases, and language difficulties in 17-100%.[89]

Dandy Walker Complex

Dandy Walker Complex (DWC) is defined as the presence of three features: cystic dilatation of the fourth ventricle, hypoplastic cerebellar vermis, and elevation of the tentorium. DWC may be isolated, or associated with other CNS abnormalities in 13-67%, and non-CNS abnormalities in 9-44% of cases.[89] A meta-analysis including 13 infants with isolated DWC and normal karyotype estimated the rate of developmental difficulties to be 58.2%, and the rate of VPS insertion 62.7%.[91] Studies of pre and postnatally diagnosed DWC are larger but vary in their definitions of DWC, and report up to a third of children having normal outcome, with normal lobulation of the vermis associated with better cognitive abilities. All children

who had normal lobulation and learning difficulties had other structural abnormalities in addition to DWC.[89]

Isolated cerebellar vermis hypoplasia

A meta-analysis involving 18 fetuses with vermian hypoplasia found developmental difficulties in between 0-33%. None required VPS.[91] One of the studies provided data up to school age, noting children with isolated vermian hypoplasia had normal outcomes.[92] In studies of cases diagnosed pre and postnatally, normal outcome was seen in 77%; affected children displayed gross and fine motor difficulties, social-communication disorders, and behavioural difficulties.[89]

Mega cisterna magna (MCM)

The MCM abnormality is defined as an enlarged cisterna magna with normal fourth ventricle, cerebellar hemispheres, and vermis.[85; 89] The rate of adverse developmental outcome in MCM is estimated around 13.8%, with study rates ranging from 0-50%.[91] A meta-analysis suggests adverse outcome in 8% of children,[89] although adult series suggest higher cognitive functions, including executive and language functions, may be affected.[85] As with other conditions, the outcome of fetuses with MCM and additional abnormalities will depend on the nature of those abnormalities, but a rule-of-thumb is that around 66% will not have developmental difficulties.[85; 89]. MCM may be the presenting feature of Joubert's syndrome where the cerebellar peduncles are prominent and there is a cleft in the midbrain, described as the "molar tooth sign", on ultrasound or MRI.[93]

Blake's Pouch Cyst

This abnormality is defined as a communication between the fourth ventricle and the posterior fossa with a normal vermis, and may reflect delayed closure of the vermis.[85] Where this is an isolated finding, developmental outcome is good and the risk of difficulties is similar to the normal population.[91]

Rhombencephalosynapsis

This rare disorder is characterised by fusion of the cerebellar hemispheres with differing degrees of vermian agenesis. It can occur in isolation or with other abnormalities, including Gomez-Lopez-Hernandez Syndrome (OMIM 601853), a condition associated with craniosynostosis, alopecia, corneal clouding, moderate to severe learning disabilities, head nodding, behavioural and sleep difficulties, and hydrocephalus. In isolated rhombencephalosynapsis, data on developmental outcome is limited. Cognitive outcomes range from normal outcome to severe learning difficulties; motor outcome is usually abnormal, including ataxia, spasticity, poor balance, and oculomotor abnormalities.[89]

Key points: the outcome data on posterior fossa abnormalities is lacking. Bilateral cerebellar hypoplasia and lesions associated with other fetal anomalies are more likely to be associated with significant developmental difficulties. DWC is associated with developmental difficulties in up to 60% of fetuses, whilst the Blake Pouch cyst gives a similar risk to the general population. A small cerebellum in early gestation may exhibit catch-up growth and appear normal later in pregnancy.

MYELOMINGOCELE (MMC)

Myelomeningocele is associated with a range of difficulties, so counselling requires a multidisciplinary approach.

Motor outcomes

The chance of ambulation in MMC is linked to the lesion level (table 4), although the functional level of a lesion may differ from its visual level on antenatal USS and iuMRI.[94-96] Overall, 63-73% of children walk to some degree, [97-99] but this may not be “normal walking”: muscle weakness, spasticity, joint abnormalities, and ataxia mean ambulation may be slow, with frequent trips or falls. 11% walk without aids, splints or orthotic support [97] and 37% of children are wholly reliant on a wheelchair.[97] Later in life, ambulant children may become

non-ambulant because of weakness, spasticity, contractures, neuropathic osteoarthropathy, obesity, progressive spinal problems like kyphoscoliosis, or because it is simply faster and easier to keep up with their peers. At 25 years of age, 33% are ambulant, reducing to 21% by 50 years. Babies with motor or sensory levels below L3 and those with quadriceps activity at birth are more likely to be walking at 50 years of age than those with higher lesions.[100] Upper limbs can be affected by weakness, poor dexterity, reduced motor speed and planning, and poor bimanual coordination, probably because of hydrocephalus, brainstem or cerebellar abnormalities, visual impairment, impaired trunk control, or scoliosis.[101]

Arnold Chiari malformation type 2, hydrocephalus, and abnormal brainstem function

Arnold-Chiari Type 2 malformations (ACM2) occur in 80-90%[99; 102] of children with MMC, and hydrocephalus in 77-84%.[102; 103] The rates of VPS insertion are 51-72%.[99; 102-105], of whom 37% require a revision in the first year of life.[97] ACM2 and hydrocephalus can compress the brainstem leading to dysphagia, stridor, aspiration, centrally-mediated apnoeas, and motor signs.[106] These can be addressed by treating the hydrocephalus in most cases, but 5-11% require ACM decompression.[97; 102; 106] Surgical treatment is 4 times more likely in thoracic than sacral lesions.[106] 1% of people with ACM2 require tracheostomy. Brainstem dysfunction can be seen in the absence of ACM2 and hydrocephalus, and may be life-limiting.[106]

Cognition and schooling

Children and adults with myelomeningocele have lower cognitive scores on testing of general cognitive abilities than the general population, but scores are typically in the normal or borderline learning difficulties range: mean IQ scores range from 71.9 - 96.6.[101; 107-110] The key factor is hydrocephalus: average IQ scores without hydrocephalus are 97.6-103.0, compared to 75-89.7 for shunted hydrocephalus.[107; 108] Around 80% of children will attend mainstream school, 20% require special school education.[111] For those with general cognitive abilities in the normal range, additional educational support in the classroom may be required because of subtle learning difficulties, poor attention/concentration,[109; 110; 112-114]

short and long term memory problems, impaired visuo-spatial/visuo-memory, and executive functioning skills.[108;115]

Bowel and bladder function

Urinary difficulties related to neurogenic bladder are frequent, and counselling should include a discussion on the likely bladder management plan. Long term, 76.8% of adults use intermittent catheterisation and 45% achieve some form of continence with or without catheterisation.[116-118] 33.3% of young adults with MMC never have urinary accidents, 12.5% less than once a month, 27.1% at least once a month but less than once a week, 14.6% once a week but not every day, and 15.0% every day. Lower lesions are associated with less accidents than higher lesions.[119]

Faecal incontinence and constipation are also common: 48.9% achieve bowel continence, 17.4% will require an antegrade colonic enema procedure, 5.1% a cecostomy button, and 2.9% a colostomy or ileostomy. Laxatives, enemas and digital stimulation or extraction may be required.[120] Faecal incontinence is strongly associated with quality of life, participation, travelling, socialising, family emotions/relationships, and finances.[121-123]

Other comorbidities

80% of individuals with MMC develop contractures that require orthopaedic intervention,[124] 15-22% have a latex allergy,[125-127], sleep-disordered breathing can be seen,[128] and progressive spinal problems may affect respiratory function.[129]

Relationships, sexual function, and fertility

23-28% of individuals with MMC will marry and 52% will not form a long-term relationship.[114;130] Between 24-51% of adults with MMC have sex regularly,[131-133] but sexual activity is less likely with higher spinal lesions. Erectile dysfunction is reported in 12-75% [134-136] and is more common in lesions above T10.[137] Sildenafil may help.[138] Sperm counts and morphology are

abnormal, with hydrocephalus a significant risk factor, so fertility may be impaired.[134] 55.5% of women report sexual dysfunction.[139; 140] Evidence shows the relationship between sexual function and health-related quality of life is weak or non-existent.[131; 133]

Adulthood

Around 94% attain high school qualifications or equivalent [114], and 8-56% complete a higher degree or technical qualification.[114; 130] Rates of employment range from 44-85%,[114; 130] but half of adults with MMC work part time because of their health, and salaries are below the national average.[114] 21-51% will live independently with or without some form of assistance.[100; 114; 130] The presence of hydrocephalus reduces the chance of independent living.[100; 114; 130] Functionally, 85% of adults with MMC can dress themselves, 65% shop for themselves, and 54% drive.[130] Overall life satisfaction is equivalent to the general population, but lower scores are found for employment, contact with friends, self-care, relationships, physical and mental health.[114]

Fetal surgery

Fetal surgery of myelomeningocele reduces the risk of hindbrain herniation and VPS insertion at both 12 months and between 5-10 years of age, improves motor function, self-care, quality of life, and family impact scores. There is no apparent benefit on adaptive behaviour or cognition.[141-143] Health care professionals should be aware of the location and referral criteria for their fetal surgery centre.

Key points: counselling of MMC should involve a multidisciplinary team with knowledge of the long-term outcomes including motor, cognition, bowel and bladder functions, educational abilities, and ability to live independently, sexual function and fertility. Advice on disability and quality of life should not be incorrectly catastrophic. Fetal surgery should be offered where appropriate.

CONCLUSIONS

There is limited evidence on neurodevelopmental outcomes of CNS abnormalities diagnosed prenatally. Predicting an individual fetus' risk for developmental difficulties is difficult. Repeated neuroimaging, viral, and genetic studies may reveal useful information, so counselling may have to occur in a stepwise manner. When giving prognostic information, health care professionals should avoid using emotive language and inappropriately catastrophic outcomes, focussing instead on best and worse-case scenarios and functional outcomes. Where prognosis is unclear, the wider multidisciplinary team or health care community may have more experience and information, which could avoid medicolegal proceedings for wrongful life or termination. Local laws on termination of pregnancy differ between countries, and health care professionals should know the laws in their own area. Discussions about termination of pregnancy should be even-handed, and any decisions prospective parents make should be respected.

Table 1: Results of selected published studies on developmental outcome in at least 100 fetuses with ventriculomegaly

Author, Year of publication (Reference)	Methodology	Definition of ventriculomegaly	*N with follow-up data*	Age at developmental assessment	Methods and definitions used	Results
Systematic review and meta-analyses						
Carta et al (2018)[36]	Systematic review and meta-analysis	Isolated severe VM ≧15.0mm without intra- or extra-cranial abnormalities, chromosomal abnormality, or fetal infections	110	3-216mo	Developmental outcomes were defined as per original authors. Severe motor disability: no independent function Children not fitting into normal or severe groups were labelled mild / moderate	Pooled proportion of deaths (stillbirth or perinatal) - 12.1%. Outcome in survivors: • Normal outcome in 41/95 (43.2%) • Mild / moderate disability 17/95 (17.9%) • Severe disability in 37/95 (38.9%)
Pagani et al, 2014[21]	Systematic review and meta-analysis	Mild VM 10-15mm without other structural abnormalities, abnormal karyotype, or congenital infection	652	Median 30 months (range 3-151mo).	Developmental outcomes were defined as per original authors.	Developmental delay in 67/652 (7.9%).
Devaseelan et al (2010)[31]	Systematic review and meta-analysis	10.1 - 15.0mm	VM 10.1 – 15mm n=586 VM 10.1 - 12.0mm n=319	Median 30 months (range 2-72mo)	Neurological abnormality defined as: *Mild* - delayed motor skills, nystagmus, mild speech impairment *Severe* - cerebral palsy, urinary incontinence, blindness, "mental retardation"	**VM 10.1 - 15.0mm:** • 5% abnormal karyotype • 1.5% positive infection screen • All VM: abnormal outcome in 14% • If infection screen and karyotype normal: abnormal outcome in 12% • Risk of abnormal development in stable VM was lower than progressive (OR 0.29). • No different in developmental outcome between all symmetrical or asymmetrical VM (OR 0.91). **VM 10.1 - 12.0mm** • 0.4% positive infection screen • 3% abnormal karyotype • Abnormal developmental outcome in 4%
Scala et al (2017)[27]	Systematic review and meta-analysis	Isolated unilateral VM 10-15mm. "Apparently isolated":	Apparently isolated unilateral VM:	Apparently isolated unilateral VM: Median 30.3mo	Developmental outcomes were defined as per original authors.	**Apparently isolated unilateral VM <15mm** • Prevalence of abnormal karyotype 0% • Prevalence of congenital infection 8.2%

		no intra- or extra-CNS structural abnormalities Truly isolated: no other structural abnormalities on pre or postnatal imaging, chromosomal abnormality or congenital infection.	Truly isolated unilateral VM: 198	(range 24.3-36.5mo) Truly isolated unilateral VM: Median 38.0 (range 27.0-49.8mo)		• Prevalence of progression of VM 5.4% • Prevalence of subsequent intra- or extra-CNS abnormalities 6.8% • Incidence of developmental abnormalities 5.4% **Truly isolated unilateral VM <15mm** • Incidence of developmental abnormalities 7.0%
Selected individual studies reporting outcome						
Li et al (2019)[22]	Prospective	Group A 10.0-12.0mm Group B 12.1-15.0mm Group C 15.1mm+ Controls: normal fetuses Isolated - no other abnormalities on MRI.	Group A n=113 Group B n=37 Group C n=10	3, 6, 12, 18 mo	Gesell Developmental Schedules Score >85: normal Score 75-85: moderately abnormal Score <75: severely delayed	**At 18months age:** Group A: • 105/113 (92.9%) normal • 6/113 (5.3%) moderate delay • 2/113 (1.8%) severe delay Group B: • 30/37 (81.1%) normal • 4/37 (10.8%) moderate delay • 3/37 (8.1%) severe delay Group C • 4/10 (40.0%) normal • 3/10% (30.0%) moderate delay • 3/10 (30.0%) severe delay Controls • 46/50 (92/0%) normal • 3/50% (6.0%) moderate delay • 1/50 (2.0%) severe delay Statistically significant differences were seen only between Group C and Controls only.
Thorup et al, 2019[25]	Retrospective, national database	Isolated mild VM: 10-15mm on USS, no evidence of other fetal abnormalities. Excluded if abnormal fetal MRI, karyotype, microarray, TORCH screen, thrombocyte	107	2-7yrs	Abnormality defined as intellectual disability, CP, ASD, epilepsy, impaired psychomotor development	Normal outcome - 101 (94.4%) Developmental disorder - 6 (5.6%) • Intellectual disability 0 • Cerebral palsy 0 • ASD 1 (0.9%) • Epilepsy 2 (1.9%)

		antibodies, postnatal structural brain or genetic diagnoses.				• Impaired psychomotor development 3 (2.8%) OR for poor outcome 2.64 (1.16 - 6.02 95% CI)
Bar-Yosef et al (2017)[23]	Prospective	Mild VM 10mm-11.9 Moderate VM 12.0-14.9mm Severe VM ≧15mm Asymmetry: ≧2mm difference between sides Exclusions: Toxoplasma or CMV infection; other abnormalities on fetal MRI, abnormal karyotype or microarray	N=133 Mild: 108 Moderate: 24 Severe: 1 Asymmetrical: 112	Median 25mo (IQR 21-26mo)	Vineland Adaptive Behaviour Scales (VABS) scores Abnormal if <85 (below 1SD from mean)	5/133 (3.8%) had scores <85 No statistical differences in VABS scores between mild and moderate VM groups, nor symmetrical and asymmetrical VM.
Chu et al (2016)[24]	Prospective	Mild 10.0 to <12.0mm Moderate 12.0 to <15.0 Severe ≥15.0mm Isolated - no intracranial or extracranial abnormalities, negative TORCH screening and karyotype (or if parents declined)	N=151 Outcome data in 66 isolated VM (41 mild, 17 moderate, 8 severe) and 85 non-isolated VM	16mo – 9yrs	Developmental review by paediatrician and telephone interview with parents Abnormal outcome defined as death, structural malformations, poor locomotor, speech or social skills, abnormal hearing or visual function, developmental or "other" anomalies	**Isolated VM** 38/41 mild IVM (92.7%), 16/17 (94.1%) moderate IVM and 5/8 (62.5%) severe IVM had normal outcome Outcome was statistically better in fetuses where VM improved. **Non-isolated VM** 55/64 (85.9%) mild VM, 12/13 (92.3%) moderate, 5/8 (62.5%) severe had normal outcome
Ouahba et al (2006)[144]	Retrospective	Mild VM 10-15mm Excluded if abnormalities on fetal MRI, TORCH screen, karyotype	N=101	Mean 54.7mo (SD2.9mo, range 19-127mo)	Neurological examination by paediatric neurologist Brunet-Lezine Psychomotor Scale 1-2 yrs McCarthy Scales of Children's Abilities 2-4 yrs WPPSI over 4 yrs If formal assessment not performed, data collected from notes or parental questionnaire over telephone. Definitions for abnormality are not given.	12 (11.9%) had developmental delay / disease 89 (88.1%) normal development Outcome worse if VM >12mm, asymmetrical bilateral VM, or if VM progressed in pregnancy

Table 2: Results of selected published studies on developmental outcome in at least 20 fetuses with antenatally diagnosed abnormalities to the corpus callosum

Author, Year of publication (Reference)	Methodology	*N with follow-up data*	Age at developmental assessment	Methods and definitions used	Results
Systematic reviews					
D'Antonia et al (2016)[39]	Systematic review and meta-analysis	N=266 isolated complete ACC N=225 isolated partial ACC	Not given	Outcomes defined according to methodology used in original paper	**Isolated complete ACC (no other structural abnormalities)** • 4.81% abnormal karyotype, 5.75 microarray • Normal outcome 76.0% (pooled proportion) • Borderline / moderate abnormal outcome 16.0% • Severely abnormal outcome 8.0% **Isolated partial ACC (no other abnormalities)** • 7.45% abnormal karyotype, 5.7% microarray • Normal outcome 71.4% (pooled proportion) • Borderline / moderate abnormal outcome 14.9% • Severely abnormal outcome 12.5% **Complete or partial isolated ACC with normal karyotype** • 5.74% clinically significant copy number variants with microarray
Sotiriadis et al (2012)[40]	Systematic review and meta-analysis	N=132 ACC Where studies subdivided according to anatomy: Complete ACC N=70 Partial ACC N=29	Not given	Outcomes defined according to methodology used in original paper	**Developmental outcome in all ACC** • Normal outcome: 71.2% • Borderline / moderate abnormal outcome: 13.6% • Severely abnormal outcome: 15.2% **Complete ACC:** • Normal outcome: 74.3% • Borderline / moderate abnormal outcome: 14.3% • Severely abnormal outcome: 11.4% **Partial ACC:** • Normal outcome: 65.5% • Borderline / moderate abnormal outcome: 6.9% • Severely abnormal outcome: 27.6%
Selected individual studies reporting outcome					

Folliot-Le Doussal et al (2018)[145]	Retrospective	N=25 isolated ACC Exclusions: antenatal exposure to alcohol, parental consanguinity, ventriculomegaly >20mm, children under 2yrs or lost to follow-up before 6yrs	"Average" 8 +/- 5 years (range 2-16yrs)	Information from reviews by paediatrician. 15 had WISC-III, WISC-IV or WPPSI-III **Normal:** no cognitive, behavioural or motor impairments and school level appropriate **Mild: S**pecific cognitive disorders with a full scale, verbal, or performance IQ 70-85, motor disorders or language disorders. **Moderate / severe:** CP, cognitive disorders with an IQ score< 70 or autism spectrum disorders	**Normal:** 9/25 (36.0%): 6 complete ACC, 3 partial. **Mild:** 13/25 (52.0%): (8 completed ACC, 2 partial ACC, 3 hypoplasia CC). All had speech delay, 5 (20%) attentional problems, 9 (36%) specific learning difficulties, 3 (12%) gross motor disorder. Verbal comprehension scores were <85 in 60%. **Moderate / severe:** 3/25 (12%), all complete ACC. All had IQ<70 and speech delay. 2 had motor delay, 1 epilepsy and ASD.
Yeh et al (2018)[146]	Retrospective	N=40 (12 isolated 28 additional abnormalities)	Median 24.8mo (range 10-60mo)	Information from review by paediatrician. Bayley Scales of Infant Development-2 (BSID-2) or Korean Infant and Child Development Test (KICDT) **Normal:** Score ≥85 on BSID-2 or ≥80 KICDT **Moderate to severe:** Score <70 on either BSID-2 or KICDT	**Normal:** 18/40 (45.0%) **Moderate / severe:** 22 (55.0%) **Isolated ACC:** 7/12 (58.3%) normal outcome. Those who were not normal had predominately language delay. 1 had motor delay. **Non-isolated ACC:** 11/28 (39.3%) normal outcome.
des Portes et al (2018)[147]	Prospective	N=34 isolated ACC 26 had complete ACC, 8 had partial ACC	Range 3-7yrs	Variety of outcome measures and formal psychological assessments depending on age.	**Normal:** 22 (64.7%) **Learning disabilities and borderline intellectual function (IQ 70-85)**:10 (29.4%) - **Severe intellectual disability (IQ<70)**: 2 (5.9%)
Mangione et al (2011)[38]	Prospective with matched controls	N=26 isolated ACC	Median 50mo (range 30-74)	**Outcome measures:** examination by paediatrician and I Child Developmental Inventory **Developmental delay:** <79 **Borderline:** 70-79 **Learning difficulties:** <70	**Normal developmental outcome:** 19/26 (73.1%) **Developmental abnormality**: 7/26 (26.9%), of whom 5/26 (19.2%) had learning difficulties and 2/26 (7.8%) borderline learning difficulties
Chadie et al (2008)[148]	Retrospective	N=20 with isolated ACC	Mean 6yrs (range 3-16yrs)	Case note review from paediatric / psychology follow-up **Moderate disabilities:** hypotonia, subtle cognitive disorders e.g. dyslexia, visuo-spatial or attention deficits, learning disabilities **Severe disabilities:** CP, IQ<70	**Normal:** 11/20 (55.0%) **Moderate disabilities:** 5/20 (25.0%) **Severe disabilities:** 4/20 (20.0%)

Table 3: Mean head fetal measurements according to gestational age, and calculated cut-off points for 2, 3, and 4 standard deviations below the mean, generated from the data produced by Chitty et al.[51]

Gestation weeks	Biparietal Diameter Measurements (BPD outer-outer) in mm					Occipito-Frontal Diameter Measurements (OFD) in mm					Head Circumference Measurements in mm				
	4SD	3SD	2SD	Mean	SD	4SD	3SD	2SD	Mean	SD	4SD	3SD	2SD	Mean	SD
20	38.0	40.7	43.4	48.8	2.7	49.7	52.8	55.9	62.1	3.1	140.1	148.7	157.3	174.5	8.6
21	41.0	43.8	46.6	52.2	2.8	54.1	57.2	60.3	66.5	3.1	151.4	160.2	169.0	186.6	8.8
22	44.3	47.1	49.9	55.5	2.8	58.0	61.2	64.4	70.8	3.2	162.5	171.5	180.5	198.5	9.0
23	47.1	50.0	52.9	58.7	2.9	61.7	65.0	68.3	74.9	3.3	172.8	182.1	191.4	210.0	9.3
24	50.2	53.1	56.0	61.8	2.9	65.4	68.8	72.2	79.0	3.4	183.2	192.7	202.2	221.2	9.5
25	52.8	55.8	58.8	64.8	3.0	68.9	72.4	75.9	82.9	3.5	193.3	203.0	212.7	232.1	9.7
26	55.4	58.5	61.6	67.8	3.1	71.8	75.5	79.2	86.6	3.7	202.6	212.6	222.6	242.6	10.0
27	58.2	61.3	64.4	70.6	3.1	75.1	78.9	82.7	90.3	3.8	211.9	222.1	232.3	252.7	10.2
28	60.6	63.8	67.0	73.4	3.2	77.7	81.7	85.7	93.7	4.0	220.9	231.3	241.7	262.5	10.4
29	63.2	66.4	69.6	76.0	3.2	80.7	84.8	88.9	97.1	4.1	229.0	239.7	250.4	271.8	10.7
30	65.4	68.7	72.0	78.6	3.3	83.0	87.3	91.6	100.2	4.3	237.1	248.0	258.9	280.7	10.9
31	67.8	71.1	74.4	81.0	3.3	85.2	89.7	94.2	103.2	4.5	244.8	255.9	267.0	289.2	11.1
32	69.7	73.1	76.5	83.3	3.4	87.3	92.0	96.7	106.1	4.7	251.7	263.1	274.5	297.3	11.4
33	71.5	75.0	78.5	85.5	3.5	88.7	93.7	98.7	108.7	5.0	258.5	270.1	281.7	304.9	11.6
34	73.6	77.1	80.6	87.6	3.5	90.4	95.6	100.8	111.2	5.2	264.8	276.6	288.4	312.0	11.8
35	75.2	78.8	82.4	89.6	3.6	91.5	97.0	102.5	113.5	5.5	270.3	282.4	294.5	318.7	12.1
36	77.1	80.7	84.3	91.5	3.6	92.4	98.2	104.0	115.6	5.8	275.6	287.9	300.2	324.8	12.3
37	78.4	82.1	85.8	93.2	3.7	93.1	99.2	105.3	117.5	6.1	280.4	292.9	305.4	330.4	12.5
38	79.6	83.4	87.2	94.8	3.8	93.5	99.9	106.3	119.1	6.4	284.3	297.1	309.9	335.5	12.8
39	81.0	84.8	88.6	96.2	3.8	93.8	100.5	107.2	120.6	6.7	288.0	301.0	314.0	340.0	13.0
40	81.9	85.8	89.7	97.5	3.9	93.9	100.9	107.9	121.9	7.0	291.2	304.4	317.6	344.0	13.2
41	83.1	87.0	90.9	98.7	3.9	93.4	100.8	108.2	123.0	7.4	293.4	306.9	320.4	347.4	13.5
42	83.7	87.7	91.7	99.7	4.0	93.0	100.7	108.4	123.8	7.7	295.5	309.2	322.9	350.3	13.7

Table Four: Rates of walking according to lesion of myelomeningocele (data from Williams et al, 1999)[98]

Level of lesion (number of participants)	**Walked (%)**	**Average Age walked**	**Number who stopped walking (age)**	**Never walked (%)**
Thoracic (35)	7 (20%)	4yr 6mo	3 (6yr 9mo)	28 (80%)
High Lumbar (10)	5 (50%)	5 yr 2mo	3 (6yr 11mo)	5 (50%)
Mid lumbar (15)	9 (60%)	5 yr 0mo	3 (7yr 0mo)	6 (40%)
Low Lumbar (45)	38 (84%)	3yr 10mo	5 (9yr 1mo)	7 (16%)
Sacral (68)	68 (100%)	2 yr 2mo	0	0 (0%)

FIGURE LEGENDS

Figure 1: Flowchart outlining the rates of other abnormalities and developmental outcome in a) ventriculomegaly 10-15mm and b) ventriculomegaly >15mm

Figure 2: Flowchart outlining the rates of other abnormalities and developmental outcome in agenesis of the corpus callosum

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