Patrick F. Chinnery and D.M. Turnbull Developmenta

Patrick F. Chinnery and D.M. Turnbull Developmental abnormalities of the central nervous system 6350 Chris M. Verity, Jane A. Hurst, and Helen V. Firth

ESSENTIALS The brain and spinal cord arise from a sheet of cells that develop through a series of distinct transformations into the final complex structure. Congenital abnormalities of the central nervous system are considered in the context of this process, which may fail at distinct stages of development. General clinical approach A rigorous approach to the diagnosis of and counselling for devel- opmental abnormalities of the central nervous system is required. Referral for specialist advice is recommended because of the far- reaching consequences of misdiagnosis. Many abnormalities can be identified by detailed ultrasonography, and magnetic resonance imaging in utero is proving to be particularly useful for accurate in- vestigation of the fetal brain. Prenatal diagnosis is available for some conditions, with noninvasive prenatal diagnosis (and preimplantation diagnosis) becoming available for some conditions where a precise genetic diagnosis is possible. In the absence of a specific diagnosis genetic advice is usually limited and empirical, but where a specific gene is implicated parental questions can often be accurately ad- dressed. Where there are strong environmental factors, it is imperative to reduce the risk to future pregnancies by taking appropriate meas- ures (e.g. folic acid or iodide supplementation before

conception). A. Malformations resulting from abnormalities in the major steps of central nervous system formation Neural tube defects Clinical features and epidemiology—neural tube defects such as spina bifida and anencephaly reflect a failure of closure of the ectoderm folds that normally fuse 18–26 days after ovulation. Prevalence rates vary greatly by geographical area but worldwide they remain among the most frequent and the most devastating congenital anomalies. Most cases are caused by interactions between genes and environ- mental factors such as nutritional folic acid, but in the presence of additional features, they may be part of a genetic disorder. Screening—many serious (open) neural tube defects lead to an in- creased concentration of α-fetoprotein in maternal serum, and at- risk women with this elevated biomarker on screening—or those with a history of an affected pregnancy—are recommended to have fetal ultrasonography from 12 weeks onwards. Prevention—the incidence of neural tube defects can be markedly reduced at a population level by preconceptual supplementation of folic acid (400 µg daily), which has been effectively introduced in some countries by fortification of foods with folic acid. Where possible, avoidance of drugs periconceptually and in pregnancy that impair folate metabolism (eg. folate antagonists, anticonvulsants such as sodium valproate). Treatment and prognosis—the major focus is on prevention, but neurosurgical procedures are employed for closure and for relief of hydrocephalus by diversion of cerebrospinal fluid through shunt procedures. The outcomes and prognosis of affected children vary greatly and surgical management remains controversial, except for those with mild abnormalities. Other developmental abnormalities of the spinal cord—these include syringomyelia, which usually presents in later life and is associated with the Chiari malformation and hydrocephalus. Agenesis of the sa- crum with abnormalities of the distal cord is associated with maternal diabetes mellitus. Disorders of regionalization of the fully formed neural tube Numerous genes, including those encoding signalling molecules that induce the expression of homeotic genes involved throughout evo- lution in regional and segmental development, are implicated in the complex process of regionalization of the neural tube. Disorders af- fecting these pathways often involve gene–environment interactions and give rise to abnormalities of the specification of cells in the fore- brain, midbrain, hindbrain, and spinal cord (e.g. holoprosencephaly). Disorders of cortical development Numerous genetic determinants have been identified for disorders of cortical development such as microcephaly and lissencephaly, which reflect abnormalities of proliferation and cellular migration (respectively). Microcephaly may also be caused by environmental influences in pregnancy, including radiation, drugs, infections and maternal hyperphenylalaninemia (a preventable factor of import- ance in the management of women with phenylketonuria). Malformations of posterior fossa structures Hindbrain development is disturbed in the Chiari II malformations and the Dandy–Walker syndrome (agenesis of the vermis, with dila- tation of the fourth ventricle and enlargement of the posterior fossa). 24.20 Developmental abnormalities of
the central nervous system Chris M. Verity, Jane A. Hurst, and Helen V. Firth

24.20 Developmental abnormalities of the central nervous system 6351 Complex malformations of the brain and cord Many types are recognized, including agenesis of the corpus callosum and porencephaly. These disorders are rare, but are increased in children with other developmental abnormalities. Agenesis or hypogenesis of the corpus callosum may be caused by mutations in a single highly penetrant gene (e.g. ARID1B; Coffin-Siris syndrome), chromosomal imbalance, and some rare metabolic syndromes (e.g. nonketotic hyperglycinaemia). Porencephaly may be a prenatal manifestation of mutations in COL4A1/2. Vascular developmental abnormalities These include Sturge–Weber syndrome (where a vascular birthmark on the face is associated with an

angioma involving the meninges overlying the cerebral cortex) cerebral cavernomas, capillary and venous malformations resulting from somatic mosaicism. B. Clinical problems associated with abnormalities of
central nervous system development Enlargement of the cerebral ventricles (ventriculomegaly) Ventriculomegaly may be discovered on antenatal scanning and may be isolated or associated with other cerebral developmental abnor- malities. Sometimes it is an early sign of hydrocephalus—this results from expansion of the ventricles secondary to a block in the normal flow pathway of cerebrospinal fluid. Intellectual disability can result from both the damage associated with ventricular expansion and other abnormalities associated with the underlying cause of the problem. Disorders of the developing brain caused
by external factors Alcohol—fetal alcohol syndrome may cause microcephaly, structural anomalies of the brain such as partial or complete agenesis of the corpus callosum, cerebellar hypoplasia, and a dysmorphic appear- ance. Fetal alcohol spectrum disorders are much more common than fetal alcohol syndrome. Drugs of abuse—there is emerging evidence that prenatal exposure to stimulants such as cocaine and methylamphetamine can affect brain development and function Congenital infections—for example, toxoplasmosis, herpes simplex, cytomegalovirus, rubella, and syphilis. Primary maternal infection is implicated in most instances; hence measures to prevent these infec- tions are important. The cerebral palsies These are an important but heterogeneous group of nonprogressive disorders of the immature brain that cause defects of movement and posture that may have associated manifestations such as deafness, seiz- ures, and learning difficulties. Several clear genetic factors have been identified, and environmental exposure to toxins such as carbon mon- oxide, alcohol, and methyl mercury may also be responsible. Although cerebral palsy has in the past been attributed to ‘asphyxia’ at birth, this view is now changing; premature infants are at a greatly increased risk. Normal development of the human central nervous system The human central nervous system (CNS), like that of all vertebrates, develops from a two-dimensional sheet of cells into a complex three-dimensional structure. A range of abnormalities results from failures at distinct stages of development. This chapter uses the normal development of the human CNS as a framework to discuss these disorders. Only structural abnormalities of the CNS that are present at birth have been included, not the numerous metabolic and degenerative disorders that can affect the infant brain. During intrauterine life the brain develops from a plate of ecto- dermal cells into the complex structure seen in the full-term infant as is shown in Fig. 24.20.1. A. Malformations resulting from abnormalities in the major steps of CNS formation Disorders of neural tube formation The nervous system develops from a tube formed when part of the em- bryonic ectoderm folds and separates from the remaining ectoderm (Fig. 24.20.2). Closure of this tube starts at a level corresponding to the future hindbrain/spinal cord junction and then proceeds towards both the head (rostrally) and the tail (caudally). This process gener- ates the entire neural tube except for the most caudal part, which is formed by thickening of the neural plate and the subsequent forma- tion of a cavity. A population of cells (the neural crest) then migrates out of the dorsal part of this tube to form the peripheral nervous system, while those that remain in the tube form the CNS. The neural tube usually fuses completely between 18 and 26 days after ovulation (32 and 40 days, respectively, after the first day of the last menstrual period). Failure of closure leads to malformations that include anen- cephaly, encephalocele, spina bifida, and spina bifida occulta. They are malformations of the neuroectoderm, which are associated to a variable extent with abnormalities of the surrounding mesodermal structures. The term ‘dysraphism’ is used when there is continuity between the posterior neuroectoderm and cutaneous ectoderm. Craniorachischisis is the most severe type of neural tube defect, in which almost the

entire brain and spinal cord are open. Epidemiology The prevalence of neural tube defects varies according to geography and race. High rates (more than 8 per 1000 births) have been reported in Northern Ireland, Egypt, India, and China. There are worldwide reports of decreasing prevalence. In England and Wales there was a substantial decline in the birth prevalence which started in the early 1970s—in 1964 the rate was 3.6/1000 births and this fell 93% to 0.3/1000 in 2004. It was estimated that 59% of the fall was due to an underlying decrease in the prevalence of neural tube defects and 34% to antenatal screening and termination of pregnancy. During this period there was an increase in dietary folate and there is evi- dence of a protective effect of adequate folate consumption, however some of the decreased prevalence remains unexplained. In England and Wales anencephaly and spina bifida have been of approximately equal prevalence, together making up 95% of all neural tube defects. Aetiology Genetic factors Most neural tube defects result from a complex interaction between several genes and environmental factors, but a minority occur as part of a Mendelian disorder (e.g. Meckel's syndrome). If one

section 24 Neurological disorders 6352 member of a family is affected by an isolated (i.e. nonsyndromic defect), there is a small increased risk in their first-degree rela- tives of c.3% for all types of neural tube defect. Major genes have been identified that cause neural tube defects in the mouse, but their relevance to human defects is still not clear. Some genes have been shown to alter risk modestly (e.g. mutations in the methylene tetrahydrofolate reductase gene are associated with elevated blood homocysteine levels in pregnant women and a twofold increased risk of neural tube defects). At this time, however, genetic investi- gations offer little in the management of families with one member having an isolated neural tube defect. Environmental factors Periconceptual multiple vitamin supplements containing folic acid have been shown to reduce substantially the incidence of neural tube defects. In England it is currently recommended that women who are planning pregnancy should take 400 µg folic acid daily before conception and during the first 12 weeks of preg- nancy. To prevent recurrence of neural tube defects a higher dose of 4–5 mg/day is recommended. In the United Kingdom, the Food Standards Agency has recommended the mandatory addition of folic acid to bread or flour. In North America fortification of cer- tain foodstuffs with folic acid has been mandatory since 1998. Since many pregnancies are unplanned, countries that have insti- tuted folic acid fortification policies have seen reductions in neural tube defects of 27–50%. Some drugs taken during pregnancy may increase the risk of neural tube defects in the fetus, including sodium valproate and folic acid antagonists such as trimethoprim, triamterene, carbamazepine, phenytoin, phenobarbitone, and primidone. Prenatal diagnosis Ultrasonography This is recommended for all at-risk women—those who have had one or more affected child and those taking drugs associated with neural tube defects in the fetus. Anencephaly can be detected by ultrasonography from week 12 of gestation and spina bifida from 16 to 20 weeks (Fig. 24.20.3a, b), although even the best ultrason- ographers may occasionally miss spina bifida, particularly in the L5-S2 region. The recent marked improvement in the resolution of fetal ultrasonography has meant that direct sampling of the amni- otic fluid (mniocentesis) is no longer performed. However, when ad- equate ultrasound images cannot be obtained, amniocentesis with measurement of α-fetoprotein and assay of neuronal acetylcholin- esterase does provide an alternative method of prenatal diagnosis. α-fetoprotein levels in maternal serum The fetal liver is the main source of α-fetoprotein, which leaks through open neural tube defects into the amniotic fluid and then into maternal blood. The consequent abnormal increase in maternal serum α-fetoprotein is best detected at 16–18 weeks of pregnancy. Maternal serum screening does not detect closed defects (those covered by skin). The widespread use of

prenatal ultrasound for fetal anomaly screening has superseded maternal serum α-fetoprotein as a screening measure in pregnancy in many countries. Cranial abnormalities of neural tube closure Anencephaly This is a lethal defect that results from failure of fusion of the rostral folds of the neural tube. The cranial vault is absent and an 5 WEEKS 11 WEEKS MIDBRAIN (MESENCEPHALON) CEREBELLUM CEREBRUM PONS DIENCEPHALON TELENCEPHALON PONS HINDBRAIN (RHOMBENCEPHALON) SPINAL CORD DIENCEPHALON TELENCEPHALON FOREBRAIN (PROSENCEPHALON) 9 MONTHS CEREBELLUM MEDULLA OBLONGATA MEDULLA OBLONGATA
Fig. 24.20.1 Diagram showing some of the key stages in normal brain development.

 angiomatous membranous mass lies on the floor of the cranium. The eyes are protuberant as a result of shallow orbits and there is variable involvement of the spinal cord. Before the advent of pre- natal diagnosis by ultrasonography most anencephalic babies were liveborn; now an increasing number of such pregnancies are ter- minated. In liveborn anencephalic babies, the initial neurological examination may be surprisingly normal if brainstem structures are reasonably intact. However, the infants usually die in hours or days. Cephaloceles A cephalocele is a herniation of the cranial contents through a skull defect. There are several subtypes: a cranial meningocele con- tains only meninges, an encephalocele contains brain tissue, and a ventriculocele contains part of the ventricle within the herniated portion of the brain. Cephaloceles are less common than anen- cephaly or spina bifida, occurring in 1 to 3 per 10 000 live births. Posterior cephaloceles are the most common group in Western countries and most are occipital encephaloceles, whereas anterior cephaloceles are more common in some parts of Asia. Anterior cephaloceles are associated with other brain abnormalities such as agenesis of the corpus callosum, abnormal gyration, or, in the case of posterior defects below the tentorium, cerebellar defects. They may be part of a recognized syndrome such as frontonasal dys- plasia. Posterior encephaloceles may be a feature of an underlying ciliopathy such as Meckel syndrome. Spinal abnormalities of neural tube closure Spina bifida This can be divided into spina bifida occulta, which consists of failure of closure of the vertebral arches without an external lesion, and spina bifida cystica in which there is a cystic lesion on the back. The lesion may be either a meningocele without neural tissue or a myelomeningocele in which the spinal cord is a component of the cyst wall. The term ‘rachischisis’ is used for the most severe defect, which is a widely patent dorsal opening of the spine, often associated with anencephaly. Myelomeningocele This spinal defect represents the abnormality found in 80–90% of children with spina bifida cystica. It is lumbosacral in about 80% of cases and consists of a sac covered with a thin membrane that may leak cerebrospinal fluid (Fig. 24.20.3c). Neurological abnormalities depend on the level of the lesion. There is usually a mixture of upper Neural plate Neural groove Notochord Neural crest cells Epidermis Neural tube Caudal/ posterior neuropore Open spina bifida Cranio- rachischisis Closure 1 Closure 3 Anencephaly Rostral neuropore 0
Fig. 24.20.2 The upper part of the diagram shows neural tube defects arising from errors in the multisite closure of the neural tube. The coloured section shows how the embryonic ectoderm separates, folds, and closes to form the neural tube. (b) (a) (c) (d) (e) Fig. 24.20.3 (a) Prenatal ultrasonography of a child with a neural tube defect, showing the ‘lemon sign’ resulting from the change in shape of the back of the skull (on the left-hand side in the image) which is associated with the Chiari II malformation described in the text. (b) Prenatal ultrasonography of a child with a neural tube defect, showing a cystic lumbar meningomyelocele in the caudal neural tube. (c) Lumbar meningomyelocele: photograph of a newborn infant. (d) Chiari I malformation and syringomyelia in an asymptomatic girl aged 11 years. Photograph of tuft of hair seen over the

lumbar region at birth. The associated central nervous system malformations are shown in (e). (e) Chiari I malformation and syringomyelia. T1-weighted sagittal MRI shows that there is herniation of the cerebellar tonsils through the foramen magnum (arrow) and a syrinx of the lower cervical spinal cord (C5–7) (arrow head). The associated tuft of lumbar hair is shown in (d).

section 24 Neurological disorders 6354 and lower motor neuron signs, disturbance of bladder and bowel sphincters, and bladder detrusor dysfunction. The sensory level cor- relates with the severity of abnormalities in the urinary tract and has prognostic significance regarding long-term disability. Higher lesions of the cord are associated with bladder outlet obstruction, dilatation of the upper urinary tract, and chronic pyelonephritis. Hydrocephalus complicates about 90% of cases of lumbosacral meningomyelocele. Usually it is associated with the Chiari II mal- formation, where there is downward displacement of the cerebellar vermis or tonsils through the foramen magnum to overlap the spinal cord. The fourth ventricle is elongated and the midbrain distorted, causing palsies from involvement of the lower cranial nerves and central apnoea (which may be misdiagnosed as epilepsy in older children). Hydrocephalus may also be due to aqueduct stenosis or have no clear structural cause. If there is evidence of progressive ven- tricular dilatation (often detected by ultrasonography) or signs of increasing intracranial pressure, insertion of a ventriculoperitoneal shunt is usually necessary. Meningocele Here there is protrusion of the meninges outside the spinal canal: the sac does not contain any neural tissue. Meningoceles account for about 5% of cases of spina bifida cystica. There is no associated hydrocephalus and the neurological examination is usually normal. They must be distinguished from meningomyeloceles because the prognosis is so different. Spina bifida occulta This term is often applied to a defect of the posterior arch of one or more lumbar or sacral vertebrae (usually L5 and S1). It is found incidentally by radiography in 25% of children admitted to hos- pital and may be a normal variant. However, if examination of the skin over the spine reveals a naevus, hairy patch (Fig. 24.20.3d), dimple, sinus, or subcutaneous mass, further evaluation including magnetic resonance imaging (MRI) of the spinal cord is indicated. Several clinical abnormalities may be found on examination. Spinal cord malformation may cause an asymmetrical lower motor neuron weakness with wasting, deformity, and diminished reflexes in the lower limb, or progressive gait disturbance with spasticity. Either presentation may be associated with disturbed bladder con- trol. Dorsal dermal sinuses may connect the skin surface to the dura or an intradural dermoid cyst. An open sinus tract can cause recurrent meningitis so ideally it should be explored and excised before infections occur. Lipomyelomeningoceles present as a bulge in the lumbosacral region, usually lateral to the midline. They con- sist of a lipoma or lipofibroma attached to a low-lying abnormal spinal cord. Diastematomyelia is the presence of a sagittal cleft that divides the spinal cord into two halves, each surrounded by its own pia mater. A bony or cartilaginous spur may transfix the cord, fixing it in a low position as the child grows. The cleft is usu- ally in the low thoracic or lumbar region, but cervical clefts have been reported. If any abnormality involving the cord or nerve roots is found there may be a good case for neurosurgical intervention. The aim is to free the spinal cord from its abnormal attachments to allow for growth and prevent further damage. Early intervention may prevent worsening motor deficits and urological complications, but the indi- cations for intervention are controversial. Management of neural tube defects The major emphasis is on primary prevention. It is recommended that women planning to conceive supplement their diet with folic acid, which reduces the risk of neural tube defects. Screening of ma- ternal serum for α-fetoprotein is possible and prenatal diagnosis by ultrasonography is available. This is discussed above. Treatment of infants with meningomyeloceles became possible with the development of

ventriculoatrial and ventriculoperitoneal shunts. In the early 1960s, it was argued that closure of the defect within 24 h of birth reduced mortality and morbidity by avoiding infection and reducing trauma to the exposed neural tissue. A se- lective approach to the surgical management of affected infants was proposed but this has been controversial. Lorber reported four ad- verse criteria that he thought were contraindications to treatment: a high level of paraplegia, clinically evident hydrocephalus at birth, lumbar kyphosis, and the presence of other major malformations. However, even using these criteria, the outcome was uncertain; many infants survived even though they did not have closure of the defect within 24 h, and some children with a supposedly good prog- nosis were left with major disabilities after surgery. Other developmental abnormalities of the spinal cord Syringomyelia This is a tubular cavitation of the spinal cord that is often associated with the Chiari I malformation and hydrocephalus (Fig. 24.20.3e). It tends to be in the cervical region but may involve the whole cord. It rarely becomes symptomatic in children. Treatment is controver- sial. Shunting of the abnormal cavity is sometimes performed and posterior fossa exploration may be undertaken if there is a Chiari I malformation. Sacral agenesis This is strongly associated with maternal diabetes mellitus. Absence of the sacrum and coccyx is usually associated with abnormalities of the lumbosacral cord. There may be arthrogryposis at birth (de- fined as a fixed deformity of one or more joints). A flaccid neuro- genic bladder causes incontinence and there are sensory and motor deficits in the legs. Sacral agenesis may also occur as part of the single gene disorder Currarino syndrome due to heterozygous mu- tation of the homeobox gene HLXB9. Disorders of regionalization Once the neural tube has developed, specification of different regions and individual cells within these regions occurs. This patterning oc- curs in both the rostrocaudal and dorsoventral axes. The three basic regions of the CNS (forebrain, midbrain, and hindbrain) develop at the rostral end of the tube, with the spinal cord more caudally. Within the developing cord the specification of the different popu- lations of neural precursors (neural crest, sensory neurons, inter- neurons, glial cells, and motor neurons) is observed in progressively more ventral locations. This process reflects the interaction between

 genes whose expression defines individual territories or cell types and diffusible signalling molecules secreted by adjacent areas of the embryo. Of particular importance are the extracellular signalling molecules such as sonic hedgehog required for ventral induction, and a family of genes called homoeotic genes. Most of these encode proteins containing a conserved homeodomain motif that binds DNA sequences involved in the regulation of expression of other genes, so controlling cell differentiation. Failure of normal development of the most rostral portion of the neural tube (the mediobasal prosencephalon) and associated struc- tures caused by disturbances in the process of ventral induction may result in various abnormalities of the brain and face. The most severe CNS abnormality is holoprosencephaly in which there is failure of the prosencephalon to separate into two cerebral hemispheres. The mildest is olfactory aplasia with no other cerebral malformations. The severity of the associated facial abnormalities tends to parallel those in the brain. In the most severe facial abnormality there is an- ophthalmia and absence of the nose. However, there may be just mild hypotelorism (closely set eyes) or a single central incisor tooth, or the face appear normal. Holoprosencephaly (prosencephaly) This occurs with a frequency of approximately 1 in 250 conceptuses and c.1 in 10 000 births. There is failure of formation of the two cere- bral hemispheres, resulting in abnormalities of varying severity. There are many possible causes that act within a short vulnerable period, because ventral induction probably occurs before 23 days. Environmental factors are important and it is at least 20 times more common in the infants of

mothers with diabetes than in the general population. In addition, there are several genetic causes, with at least 12 genetic loci and 9 holoprosencephaly (HPE) genes identified in humans. One (HPE3 on chromosome 7q36) is the sonic hedgehog gene, and mutations in PTCH, the receptor for sonic hedgehog, have also been found in some individuals with holoprosencephaly. Many other genes are implicated in the pathogenesis of holoprosencephaly and it is associated with chromosomal abnormalities that include trisomy and other abnormalities of chromosome 13, partial deletion of the short arm of chromosome 18, ring chromosome 18, and par- tial trisomy of chromosome 7. In alobar holoprosencephaly, the completely undivided fore- brain is in the shape of a horseshoe surrounding a single cavity. The thalami are fused but the brain stem and cerebellum are well developed. The associated facial abnormalities are severe— there may be anophthalmia or cyclopia in which there is a single orbit. In holoprosencephaly with median cleft lip there is marked hypotelorism. In semilobar holoprosencephaly the brain is div- ided into two hemispheres posteriorly but anteriorly the two hemi- spheres are fused (Fig. 24.20.4). In lobar holoprosencephaly there is almost complete separation of the hemispheres and the face may be normal. The head is usually microcephalic unless there is associated hydrocephalus. In some families in which the condition is inherited in autosomal dominant pattern, the severity can be variable, with some family members having only minor features such as a single central incisor, and others with severe holoprosencephaly. When providing genetic counselling it is therefore important to look for minor signs in both parents of an affected child. The signs include orbital hypotelorism, median cleft lip, flat nose with or without a single nostril, anosmia, and a single central incisor. Prenatal diagnosis can be made by ultra- sonography from week 16 of pregnancy, with orbital hypotelorism an important feature for antenatal diagnosis. The most severely affected infants die in the neonatal period. Less severely affected patients may live for months or years. The survivors often develop infantile spasms or other seizures. Some patients with significant structural abnormalities may survive to adulthood but usually there are severe learning difficulties. Associated anomalies suggest a syndromic cause (e.g. Trisomy 13) and include congenital heart disease, scalp defects, and polydactyly. Disorders of cortical development Modern brain imaging, in particular MRI, has resulted in the identi- fication of many previously unrecognized developmental abnormal- ities of the cerebral cortex. The best characterized of these arise from defects in one of two basic processes in cortical development. The first is the proliferation of the stem cell population which generates all the neurons required for the cortex. This occurs throughout fetal development in the region next to the ventricle (germinal layer). The second is the migration of the newly formed neurons away from this ventricular region into the overlying cortex to form appropriate con- nections with other neurons. Abnormalities in migration are shown schematically in Fig. 24.20.5. Disorders of proliferation Microcephaly A failure of proliferation results in a reduced number of cells, causing a head that is disproportionately small (less than the 0.4th centile) in relation to the rest of the body. This microcephaly is often associated with significant additional abnormalities of the nervous system such as pyramidal tract signs and learning difficulties. Microcephaly is a feature of many genetically determined developmental disorders/syn- dromes. Autosomal recessive primary microcephaly is the term used to describe a genetically determined form of microcephaly previously known as ‘microcephaly vera’, with a severe and nonprogressive re- duction in head circumference (more that four standard deviations (b) (a) Fig. 24.20.4 (a) Semilobar holoprosencephaly in a girl aged 2 years imaged with T1-weighted sagittal MRI. This midline view shows absence of the corpus callosum and fusion of the frontal lobes. (b) Semilobar holoprosencephaly in the same patient using T2-weighted axial MRI. There is fusion of the frontal lobes of both cerebral hemispheres and a common central ventricle.

section 24 Neurological disorders 6356 below the mean for age) associated with mild-to-moderate learning disability but normal height, weight, and appearance. Many of the genes identified encode centrosomal proteins that are crucial for cell division. In many types of genetic microcephaly the head size may not become abnormal until as late as 32–34 weeks of gestation or even after birth. Severe microcephaly may also be a feature of a more gen- eralized disorder of growth (e.g. microcephalic primordial dwarfism where birth weight is typically <2 kg); this is a genetically heteroge- neous group due to genes encoding proteins involved in fundamental cellular processes including genome replication, DNA damage, re- sponse mRNA splicing, and centrosome function Nongenetic causes of microcephaly include ionizing radiation in the first two trimesters of the pregnancy, intrauterine infections, alcohol, drugs, and other chemicals, circulatory disturbance, and perinatal hypoxic–ischaemic events. In 2016 there was an epidemic of microcephaly in Central and South America associated with Zika virus infection in pregnancy. Poor dietary control in mothers with phenylketonuria is also an important and preventable cause of microcephaly, because the fetal brain is very sensitive to the toxic effects of phenylalanine. When there is a significant perinatal insult to the brain, the head circumference may be normal at birth, with subsequent failure of growth in the first few months of life. Macrocephaly The term ‘macrocephaly’ is used when the head circumference is above the normal range for the age, sex, and race of the child. This may result from abnormalities outside the brain parenchyma such as hydrocephalus, arachnoid cysts, congenital abnormal- ities of the cerebral veins, fluid collections over the surface of the brain, or abnormalities of the skull. Cranial imaging is necessary to make the diagnosis. The subsequent discussion deals only with megalencephaly, which is increased size of the brain itself. Although many normal individuals have large heads, megalencephaly can be associated with significant learning difficul- ties, autism, neurological abnormalities, and seizures, and this com- bination of features can have a genetic basis. The brains may have bulky gyri and usually all parts of the cerebrum are diffusely enlarged, with normal-sized or mildly enlarged ventricles. Occasionally, par- ticular parts of the brain such as the cerebellum are disproportion- ately large. No consistent microscopic alterations are reported in the cortex, but minor anomalies such as small heterotopias may be found. The abnormality may be part of a specific disorder, for ex- ample, one of the neurocutaneous syndromes, an overgrowth dis- order such as Sotos’ syndrome (OMIM 117550), or Greig syndrome due to GLI3 mutation. Large heads can run in families (‘familial megalencephaly’), in some of which there may be no abnormalities, and it is important to check the head circumference of the parents. Hemimegalencephaly or unilateral megalencephaly may involve all parts of the brain on the same side or there may be enlargement of one hemisphere only. This can be associated with other neurological problems such as intractable seizures. It may also be associated with marked developmental delay, hemiparesis, and overgrowth of one side of the face. Some children with hemimegalencephaly have the disorder due to a somatic mutation (a postzygotic mutation arising several divisions after fertilization) that affects a percentage of cells in the developing baby, e.g. megalencephaly-capillary malformation-polymicrogyria syndrome due to somatic mutation in the PIK3CA gene. Disorders of migration Migration defects occur when neurons generated by the division of stem cells in the ventricular region fail to reach their intended destination in the cerebral cortex. The different classes of defect are illustrated schematically in Fig. 24.20.5. If neurons fail to leave stem cell neuronal precursor Normal cortical development Type II – Lissencephaly Type I – Lissencephaly Periventricular Heterotopias Fig. 24.20.5 Diagrammatic representation of the cerebral cortex showing normal development and neuronal migration defects. In type I lissencephaly neurons fail to reach their intended destination. In type II lissencephaly there is overmigration of neuroglial precursors through a disrupted pial-glial limiting membrane,

resulting in nodules of ectopic neurons. If neurons fail to leave the ventricular zone entirely, periventricular heterotopias result.

24.20 Developmental abnormalities of the central nervous system 6357 the ventricular zone entirely, periventricular heterotopias result. If neurons leave the ventricular zone but then fail to complete their migration in the cortex, this causes a group of disorders of varying severity. There may be complete absence of gyri, in which case the term ‘agyria’ is used. Pachygyria describes a reduced number of broadened and flat gyri with less folding of the cortex than normal. There may be varying degrees of agyria–pachygyria in the same brain. The term ‘lissencephaly’ (Greek: smooth brain) is commonly used to describe the spectrum of malformations from complete agyria to regional pachygyria. If, however, only a subpopulation of neurons is affected and the others complete their migration normally, this results in nodular or subcortical band heterotopias. Migration disorders are found as part of recognized genetic syndromes and there are also acquired types as a result of intrauterine infections, circulatory disturbances, and toxins (al- cohol or phenytoin, for example). The classification of these dis- orders is evolving as a result of rapid advances in brain imaging and molecular biology. Type I or classic lissencephaly This is the most common type and is characterized by a smooth or almost smooth cerebral surface. The cortex is thickened (10–20 mm) usually with no other major brain malformations, although agenesis of the corpus callosum or severe cerebellar hypoplasia can be seen due, in the latter, to mutations in the reelin (RELN) gene. Infants with type I or classic lissencephaly may be divided into those who have the isolated lissencephaly sequence with no dysmorphic features (the majority) and those with the dysmorphic features of the Miller–Dieker syndrome (OMIM 247200). Genes causing type I lissencephaly in humans include: PAFAH1B1 (LIS1), TUBA1A, and DCX. DCX (double cortin) is on the X chromosome, explaining why inheritance of lissencephaly is in some cases X-linked. While affected males in these families show the full isolated lissencephaly sequence pheno- type, carrier females can show band heterotopia, in which a subset of neurons fails to complete migration and forms bilateral sym- metrical ribbons of grey matter in the centrum semiovale. This is thought to reflect X inactivation of the normal DCX gene in these neurons, while those that inactivate the mutation-containing X chromosome migrate normally. In Miller–Dieker syndrome, there is a severe seizure disorder with severe/profound hypotonia and developmental delay ac- companied by postnatal growth deficiency and microcephaly. The dysmorphic features include a tall narrow forehead, a depressed nasal bridge, anteverted nares, midfacial hypoplasia, a prom- inent upper lip with a thin vermilion border, retrognathism, and hypervascularization of the retina. About 50–70% of cases have a deletion of chromosome 17p13.3 visible by light microscopy and almost all the remainder have a submicroscopic deletion demon- strable by genomic array. Heterozygous deletion of the PAFAH1B1 (LIS1) gene causes the lissencephaly seen in the Miller–Dieker syndrome and the facial dysmorphism may be caused by loss of adjacent genes. The diagnosis of type I lissencephaly is made by CT or MRI, which shows a thick cortical plate with no or few sulci separated from the white matter by an undulating border (Fig. 24.20.6a). Prenatal diag- nosis is not possible by ultrasonography before 24 weeks because tertiary sulci do not appear before then. Type II or ‘cobblestone’ lissencephaly This is a completely different malformation from type I lissencephaly. The smooth cortex has a granular surface and the meninges are thickened due to mesenchymal proliferation. The cerebellum is small with an absent vermis and the pyramidal tracts are usually absent. Hydrocephalus is present in 75% of cases. Microscopically there is complete disorganization of the cortex which consists of neurons separated by bundles of gliomesenchymal tissue continuous with the meninges. More deeply, there is a thin layer of white matter lying above

islands of heterotopic grey matter. These abnormalities are thought to result from overmigration of neuroglial precursors through a dis- rupted pial-glial limiting membrane, resulting in the nodules of ec- topic neurons that generate the granular texture of the brain. This is caused in some cases by abnormalities of adhesion molecules, such as dystroglycan—responsible for anchoring the endfeet of the glial cells that define the migratory pathway of the neurons to the over- lying pial membrane. As these same adhesion molecules are required for attachment of muscle fibres and retinal cells to their overlying basement membranes, many type II lissencephaly syndromes are associated with muscle and eye abnormalities. These disorders con- stitute a group of autosomal recessive congenital muscular dystro- phies associated with defects in O-glycosylation of α-dystroglycan, which includes Walker–Warburg syndrome, Fukuyama cerebral and muscular dystrophy, and muscle–eye–brain disease. The most severe forms of these diseases often have a fetal presentation. Elevation of creatinine kinase suggests this condition and targets genetic analysis. Heterotopias Periventricular heterotopias are abnormally placed groups of neurons that have failed to start or complete their migration. These often cause seizures and may be associated with intellectual im- pairment. Failure of migration results in the neurons remaining in the ventricular region, under the ependymal cells that line the ventricle, generating periventricular or subependymal heterotopias (see Fig. 24.20.6b). These may be the result of single gene disorders such as a mutation in the filamin A (FLNA) gene on the X chromo- some. Filamin protein reorganizes the cytoskeleton, consistent with (b) (a) Fig. 24.20.6 (a) Lissencephaly type I in a boy with a de novo deletion in the LIS1 gene on chromosome 17. T1-weighted axial MRI shows agyria of the parietal and occipital lobes of the brain, with pachygyria of the frontal lobes. This anterior-to-posterior severity gradient is characteristic of LIS1 deletions or mutations. (b) Nodular heterotopias in a boy aged 13 years. The T2-weighted axial image shows that the nodular heterotopias are subependymal (arrow) and subcortical (arrow head).

section 24 Neurological disorders 6358 a role in cell migration. Families with periventricular heterotopia have been described in which females are affected whereas affected males appear to die before or soon after birth. Just as in DCX mu- tations, discussed earlier, it is likely that the heterotopias present in affected females result from X inactivation of the normal FLNA gene in those cells, whereas those cells inactivating the abnormal FLNA gene migrate normally. Males have only one X chromosome and so all cells will fail to migrate—a lethal phenotype. A failure to complete migration generates subcortical heterotopias, which can be divided into two groups: nodular heterotopias of grey matter are found in association with other migration disorders (see Fig. 24.20.6b) and subcortical laminar heterotopias, also known as band heterotopias, as discussed above. Nonlissencephalic cortical dysgenesis Polymicrogyria is the most important type of abnormality in this section. The surface of the cortex can be relatively smooth, resem- bling pachygyria, because the small gyri pile up on each other to form a thickened cortex. The histology of polymicrogyria varies, sug- gesting that different migration defects are responsible for the failure to form the normal six-layered cortex. It is suggested that the devel- opmental disturbance occurs near the fifth month of pregnancy. Case reports of polymicrogyria in the infant brain after maternal trauma or asphyxiation during the pregnancy suggest that the abnormality may sometimes be due to failure of cerebral perfusion with resulting hypoxia. The clinical manifestations of polymicrogyria depend on the location and extent of the abnormalities. Small patches may be found incidentally in the absence of symptoms, but there may be involvement of the whole cortex, resulting in developmental delay. A substantial proportion of cases have a genetic basis (e.g. GPR56 causing bilateral perisylvian polymicrogyria) or an inherited meta- bolic disorder such as Zellweger

syndrome, so referral for a clinical genetics opinion is recommended. Other disorders of cortical development Cortical microdysgenesis or dyplasia Macroscopic and microscopic abnormalities of cortical structure have been described in the brains of patients with epilepsy or learning difficulties, and have also been reported in autism, schizophrenia, and fetal alcohol syndrome. These abnormalities include persistence of the subpial layer, aggregates of large neurons in the plexiform zone, a frag- mented appearance of the superficial neuronal layers, excess ectopic cells in the cortex, and excess numbers of cells in the molecular layer. Their causes and the extent to which these cause global abnormalities in brain function remain unknown, as such abnormalities can be found in normal individuals. However, they do cause cortical excitability in generalized epilepsy. Focal cortical dysplasias are an important cause of early onset seizures that may be focal or generalized (Fig. 24.20.7) and patients with refractory epilepsy should therefore have the best possible neuroimaging even if they have generalized seizures. Disorders of cortical organization Once migration is complete, the neurons begin the complex tasks of elaborating dendrites and axons, and forming synapses to establish the connectivity required for correct functioning of the human brain. These tasks remain poorly understood, but there is increasing interest in their abnormalities because they may represent important causes of epilepsy and developmental delay. Although subtle compared with the gross anatomical defects created by the migration disorders, it is likely that this group of disorders will become increasingly well rec- ognized as imaging and other investigative techniques improve. Malformations of posterior fossa structures Once regionalization has been completed, the developmental pro- cesses that generate the cerebellum and brain stem are distinct from those responsible for cortical development. Consequently, although some genetic mutations result in abnormalities in both anterior and posterior fossae (e.g. RELN and the type II lissencephalies), there are several specific posterior fossa malformations. These are now identified using prenatal ultrasonography and MRI, which is superior to CT for showing posterior fossa structures. Recently, cilia-related genes have been implicated in several congenital dis- orders (ciliopathies) characterized by cerebellar abnormalities such as Joubert syndrome, Meckel–Gruber syndrome, Bardet–Biedl (c) (b) (a) Fig. 24.20.7 (a) Cortical dysplasia in a boy aged 4 years. Focal seizures started at 1 year of age and consisted of a giggle, flexion of the left arm, and a vacant stare. T1-weighted coronal MRI shows cortical dysplasia in the right parietal region (arrow). (b) The same patient. On T2-weighted axial MRI, the cortical dysplasia is marked with an arrow. (c) Cortical dysplasia in a boy aged 3 years. Seizures commenced at 9 months of age and consisted of daytime absences and nocturnal generalized tonic–clonic seizures. A T2-weighted coronal MRI shows an abnormal fissure in the cortex on the right (arrow). The right lateral ventricle is abnormal in size and shape.

 syndrome, and orofaciodigital syndrome, suggesting that cilia play an important role in cerebellar development. Aplasia and hypoplasia of the cerebellum This is a heterogeneous group of conditions that affect cerebellar de- velopment in various ways; total cerebellar aplasia is exceptional and unilateral hypoplasia occurs very infrequently. Neocerebellar aplasia (Fig. 24.20.8a) is characterized by a small vermis and extreme small- ness or absence of the cerebellar hemispheres, except for persistent floccules. There may be associated anomalies in the brain stem such as dysplasia of the inferior olivary nucleus and other brainstem nuclei. Many cases are associated with genetic syndromes, some of which (including most of the ciliopathies) are autosomal reces- sive and have a high recurrence risk. Recent attention has been drawn to a group of disorders classified under the broad headings of pontocerebellar hypoplasia or olivopontocerebellar atrophy. Pontocerebellar

hypoplasia is found in carbohydrate-deficient glycoprotein syndromes, dystroglycanopathies (Walker–Warburg syndrome, Fukuyama syndrome, and muscle–eye–brain diseases— see earlier), disorders of the glycosylphosphatidylinositol (GPI) complex that anchors extracellular proteins to the plasma membrane, and various rare mitochondrial disorders. MRI dem- onstrates cerebellar hypoplasia often with a hypoplastic ventral pons. Pontocerebellar hypoplasia type 1 (caused by biallelic muta tion of the VRK1 gene) is characterized by central and peripheral motor dysfunction associated with anterior horn cell degeneration resembling infantile spinal muscular atrophy (SMA type 1). The Chiari malformations There are four types: the most common, Chiari II malformation, is usually associated with a meningomyelocele and is dealt with earlier under neural tube defects. In Chiari I malformation there is down- ward displacement of the lower cerebellum, including the tonsils. It rarely causes symptoms in childhood but may be associated with hydrocephalus and syringomyelia. Chiari III malformation con- sists of downward displacement of the cerebellum into a posterior encephalocele and Chiari IV malformation is a form of cerebellar hypoplasia. Chiari malformation may also occur as a component of various rare genetic disorders including Apert syndrome and Pfeiffer syndrome. Abnormalities of the vermis Dandy–Walker malformation and Dandy–Walker variant The Dandy–Walker malformation (Fig. 24.20.8b) consists of the following triad: • complete or partial agenesis of the vermis • cystic dilatation of the fourth ventricle • enlarged posterior fossa with upward displacement of lateral sinuses, tentorium, and torcula, while a variant form lacks pos- terior fossa enlargement There is an association between Dandy–Walker malformation and chromosomal abnormalities including trisomies 13 and 18, and the malformation is a feature of many rare genetic disorders. Prenatal ultrasound studies may reveal the abnormality at 18 weeks' ges- tation, 3 weeks after the development of the inferior vermis, and show that most fetuses with the Dandy–Walker malformation have other anomalies including ventriculomegaly, holoprosencephaly, agenesis of the corpus callosum, occipital encephaloceles, and struc- tural heart defects. Fetal MRI may be helpful in clarifying the nature of the brain anomaly. The clinical outcome of babies presenting with Dandy–Walker malformation ranges from severe learning disabilities and physical impairments to normal development. The abnormality is often rec- ognized only when the infant is investigated for signs of hydroceph- alus, which may not become apparent until late in the first year of life, or later in life with learning difficulties. Cerebellar signs tend not to be prominent, but cranial nerve palsies, nystagmus, and truncal ataxia have been described. Radiological diagnosis is relatively straightforward for the com- plete Dandy–Walker malformation, although without sagittal MRI the variant may be difficult to distinguish from a prominent cisterna magna or a retrocerebellar arachnoid cyst. Joubert syndrome This rare autosomal recessive ciliopathy is characterized by brain- stem and cerebellar malformations resulting in a 'molar tooth' ap- pearance on cranial MRI together with variable involvement of (a) (b) (c) (d) Fig. 24.20.8 (a) Cerebellar hypoplasia in a boy aged 5 years, who was born preterm at 26 weeks of gestation, with no neurological problems apart from absence seizures of unknown cause. T1-weighted coronal MRI shows almost complete absence of the cerebellar hemispheres and hypoplasia of the cerebellar vermis. (b) Dandy–Walker malformation in a 1-year-old girl. Axial CT shows absence of the roof of the fourth ventricle. A large cyst is continuous with the fourth ventricle and fills the posterior fossa. (c) Joubert syndrome in a girl aged 10 years. T1-weighted sagittal MRI shows that the superior cerebellar peduncles run horizontally (arrow) and the cerebellar vermis is absent. (d) Joubert syndrome in a girl aged 9 months who was hypotonic and visually unresponsive, with 'wandering' nystagmus. Axial CT shows the superior cerebellar peduncles (arrows) run horizontally and stand out because of the absence of the vermis ('molar tooth sign'). The prominent fourth ventricle has a typical shape (sometimes looking like a 'bat's

wing’).

section 24 Neurological disorders 6360 other body systems (e.g. renal cystic disease, retinal dystrophy). It is genetically heterogeneous and many genes encoding cilial and basal- body proteins have now been implicated. Features include absence or hypoplasia of the posteroinferior part of the cerebellar vermis. In some cases, enlargement of the fourth ventricle and the cisterna magna has been reported. Microscopically, heterotopias have been seen in the cerebellar hemispheres with fragmentation of the den- tate nuclei. Brainstem abnormalities include absence of pyramidal decussation, abnormal inferior olivary nuclei, and subtle dysplasias in the nuclei of the solitary and descending trigeminal tracts and of the dorsal columns. The common clinical abnormalities are marked hypotonia (particularly in the neonatal period and infancy), poor balance (walking occurs in 50% of cases and is late—at approximately 4 years), and variable cognitive problems (some affected children are unable to talk but others develop language, read, and write). The associated abnormalities are dysmorphic facial features, episodic hyperpnoea and/or apnoea in up to 75% of patients (most marked in the neonatal period), eye abnormalities, and microcystic renal disease. Typically, CT or MRI shows the ‘molar tooth’ sign in the axial plane, which consists of: (1) a deeper than normal posterior interpeduncular fossa, (2) prominent or thick- ened superior cerebellar peduncles, and (3) vermian hypoplasia or dysplasia. MRI in the coronal and axial plane shows clefting of the vermis; in the sagittal plane it shows an abnormally shaped and rostrally placed fourth ventricle (Fig. 24.20.8c, d). Renal sur- veillance is indicated as some children have cystic renal disease which may lead to renal failure. Complex malformations of the CNS Thus far we have presented disorders of the cerebral cortex resulting from defects in a single part of brain development. However, this is oversimplistic because many of these developmental processes occur simultaneously (and will therefore all be affected by terato- gens or other extrinsic perturbations) or rely on the timely comple- tion of a prior step for their initiation. As a result, there are several well-recognized malformations that cannot be ascribed precisely to abnormalities in one step or the major steps in development and result in more complex defects. Agenesis of the corpus callosum The true prevalence of this abnormality is not accurately known because it can be present without any symptoms. Estimated preva- lence has varied from 0.05 per 10 000 to 70 per 10 000 in the general population, increasing to 230 per 10 000 in children with develop- mental disabilities. In the normal developing brain, the first fibres cross the midline at 11–12 weeks to form the corpus callosum, which extends back in the occipital direction to assume the adult form by 18–20 weeks. There are two types of ‘true’ callosal agenesis: defects in which axons are unable to cross the midline and defects in which the commissural axons or their parent cell bodies fail to form in the cerebral cortex. The former is probably the most common type, al- though the latter is seen in the Walker–Warburg syndrome and other types of lissencephaly. There are also two secondary types: absence associated with major malformations of the embryonic forebrain, such as holoprosencephaly, and degeneration or atrophy, as is seen in some syndromes in which the corpus callosum is thinned but not shortened. When agenesis of the corpus callosum is the only lesion there may be no symptoms, although tests of perception and lan- guage may demonstrate disturbances of integration of hemispher- ical function. However, even if there is no clearly defined syndrome, some patients have learning disabilities, seizures, or cerebral palsy. Agenesis or hypoplasia of the corpus callosum may occur as a component of many single gene disorders (e.g. ARID1B syndrome (Coffin-Siris syndrome), ARX syndrome) and FOXG1. It has also been associated with several chromosomal imbalances. Callosal agenesis may occur in several metabolic disorders including non- ketotic hyperglycinaemia. Diagnosis is based on brain imaging (Fig. 24.20.9). The

abnormal- ities that can be found are widely spaced parallel lateral ventricles, colpocephaly (enlarged posterior horns of the lateral ventricles), upward displacement of the third ventricle, absent callosal tissue, or midline dorsal cyst. Prenatal ultrasonography allows diagnosis from week 20 of gestation. After birth MRI is best because it gives sagittal views of the corpus callosum. The scan should be care- fully reviewed for other midline anomalies (such as agenesis of the (c) (b) (a) Fig. 24.20.9 (a) Normal brain in a girl aged 2 years. A T1-weighted sagittal MRI shows normal corpus callosum and cingulate gyrus (arrow). (b) Agenesis of the corpus callosum in a girl aged 6 years who has microcephaly and moderate learning difficulties. A T1-weighted sagittal MRI shows absence of the corpus callosum and of the cingulate gyrus, which normally runs parallel to the corpus callosum. (c) Agenesis of the corpus callosum in the same girl as in (b). Axial CT shows typical appearance of parallel lateral cerebral ventricles, with divergence of the anterior horns of the ventricles and colpocephaly (dilated posterior part of the lateral ventricles).

 septum pellucidum) or generalized defects (such as lissencephaly). The eyes may show optic nerve hypoplasia (as seen in septo-optic dysplasia) or choroidal lacunae (as seen in Aicardi syndrome). Neonates with seizures or other significant neurological problems may have an underlying metabolic disorder, for example, nonketotic hyperglycinaemia (raised cerebrospinal fluid glycine) or a mitochon- drial disease sometimes withraised cerebrospinal fluid lactate). Porencephaly The term ‘porencephaly’ is often used indiscriminately for all large cavities in the brains of infants, but should be reserved for circum- scribed hemispherical necrosis that occurs in utero before the adult features of the hemisphere are fully developed (Fig. 24.20.10b). The developmental origin of such lesions is shown by their smooth walls and disturbances in the development of the adjoining cortex. These disturbances may take the form of polymicrogyria or local distor- tion of the gyral pattern. In contrast, areas of damage resulting from insults in the terminal phase of the pregnancy or in postnatal life have irregular shaggy walls, and do not alter the gyral environment except by atrophy or scarring. Porencephaly may be an important prenatal presentation of a genetic disorder caused by heterozygous mutation in the COL4A1/2 genes. Schizencephaly This term is used to describe clefts that traverse the full thickness of the hemisphere, connecting the ventricle to the subarachnoid space. They are described as type I or ‘fused lip’ when the walls of the cleft are opposed, and type II or ‘open lip’ when cerebrospinal fluid sep- arates the walls (Fig. 24.20.10d). Some authors think that the clefts are usually the result of destruction of brain tissue and the term ‘porencephaly’ should be used for them all. However, there is now evidence that some of them are genetic, because familial and spor- adic cases have been recognized in association with mutations in the homeobox gene EMX2. This is one of the vertebrate homeobox genes thought to play a role in patterning the forebrain. The clefts are frequently bilateral and symmetrical, the most severe form being large bilateral defects. Even when unilateral, they are often combined with cortical dysplasia of the opposite hemisphere. Clinical features are variable, depending on the site and size of the lesion. Epilepsy is common and there may be hemiplegia, quadriplegia, and learning difficulties of variable degree. The diagnosis is made by MRI. Hydranencephaly In this condition, the cerebral hemispheres are almost completely replaced by fluid-filled sacs. The defect typically corresponds to the territory of the anterior and middle cerebral arteries, although the major cranial arteries do not usually show evidence of obstruction. Preservation of the temporal lobes and the tentorial parts of the oc- cipital lobes is common, but the extent of preservation of the basal ganglia varies. The cause of hydranencephaly is not clear in many cases. It has been described after intoxication of pregnant women with gas at about week 25 of gestation. It can result from

intrauterine infections and has been described in association with a proliferative vasculopathy due to biallelic mutation of the FLVCR2 gene. Affected infants may be born after a normal pregnancy and be surprisingly normal on neurological examination for the first few weeks of life. Gradually they become hypertonic and irritable and develop infantile spasms, which is surprising because of the almost complete lack of cerebral hemispheres. The head may en- large because of associated hydrocephalus. The diagnosis can be made by transillumination of the skull, which lights up like a lan- tern in a darkened room. Similar appearances can be caused by (a) (b) (c) (d) Fig. 24.20.10 (a) Cerebral palsy: spastic diplegia. Probable periventricular leucomalacia in a girl aged 6 years. There was threatened premature labour at 29 and 32 weeks, but she was born at term with no perinatal problems. She walked late with a diplegic gait. T2-weighted axial MRI shows abnormal signal change lateral to the body of the left lateral ventricle and posterolateral to the posterior horn of the left lateral ventricle (arrow). This is a characteristic distribution of periventricular leucomalacia, but such appearances should be interpreted with caution because there are other causes of white matter abnormalities in children (e.g. the leukodystrophies). (b) Cerebral palsy: left hemiplegia. Porencephalic cyst in a boy aged 18 months. He was delivered by forceps at 38 weeks with no resuscitation, but nasogastric feeding for several days after birth. At 10 months of age he was not moving the left arm normally. T2-weighted axial MRI shows that there is dilatation of the anterior horn of the right lateral ventricle with loss of overlying cerebral cortex and a small periventricular cyst adjacent to the anterior horn of the right lateral ventricle. These abnormalities may result from periventricular leucomalacia. Such loss of tissue due to in utero damage of the developing brain is called a porencephalic cyst. (c) Cerebral palsy: left hemiplegia. Tissue loss in middle cerebral artery territory in a young woman aged 17 years. There were no perinatal problems, reduced movement of the left arm from 6 months of age, nocturnal generalized tonic–clonic seizures from 4 years of age, normal intelligence, abnormal posture of the left hand, and shortening of the left leg. T1-weighted axial MRI shows that there is a loculated cystic lesion in the distribution of the supply of the right middle cerebral artery. Also ex vacuo enlargement of the right lateral ventricle and small ipsilateral right hemicranium. (d) Open-lip schizencephaly in a 49-year-old woman. An axial CT scan shows that there is a wide cleft joining the right lateral ventricle to the subarachnoid space.

section 24 Neurological disorders 6362 hydrocephalus with a very thin cortical mantle, so MRI is indicated to confirm the diagnosis. Infants with hydranencephaly often die in a few months, but they may survive for several years and may need a ventriculoperitoneal cerebrospinal fluid shunt if there is progres- sive hydrocephalus. Septo-optic dysplasia This is the association of optic nerve hypoplasia with absence of the septum pellucidum. Disturbances of the hypothalamopituitary axis may occur. The most severely affected patients are blind and have severe learning difficulties. The optic discs have a character- istic double contour: the true disc at the centre is small and there is a peripheral ring about the size of a normal optic nerve head. It is im- portant to search for evidence of endocrine disturbance when these abnormal discs are identified—deficiencies of growth hormone, corticotrophin, luteinizing hormone, and follicle-stimulating hor- mone have been described, together with hypoglycaemia and dia- betes insipidus. Most cases are sporadic. Also some sporadic cases of the more common mild forms of pituitary hypoplasia are associated with heterozygous mutations of the HESX1 gene. Vascular developmental anomalies Sturge–Weber syndrome occurs due to a somatic gain of function R183Q mutation in the GNAQ gene and is characterized by an ex- tensive port-wine stain vascular birthmark affecting the face. If this occurs in the distribution of the trigeminal nerve, there may be in- volvement of underlying cortex and associated epilepsy. Cerebral cavernomas are developmental anomalies of the cerebral

vasculature. When multiple, they are termed congenital cavernous malformations and may be caused by germline mutation in the KRIT1, CCM2, or PCD10 gene Arteriovenous malformations (AVMs) may be sporadic and can be caused by a somatic mutation as in Parkes–Weber syndrome where a cutaneous flush is accompanied by underlying multiple micro arteriovenous fistulas often associated with soft tissue and skeletal hypertrophy. Capillary malformation-arteriovenous malformation (CM-AVM) is an autosomal dominant disorder characterized by multifocal ca- pillary malformations and a high risk for fast-flow lesions that may occur anywhere in the body including vein of Galen malformation. CM-AVM is caused by a germline mutation in the RASA1 gene. B. Clinical problems associated with abnormalities of CNS development In the previous sections, we classified the malformations of the developing brain by their anatomical location, taking advantage of the advances in imaging that have greatly increased our ability to diagnose these conditions. However, clinical problems can be asso- ciated with factors that have a more generalized impact on the CNS, and some of the most important of these are considered next. Fetal cerebral ventriculomegaly Dilatation of the lateral cerebral ventricles is the most common CNS abnormality identified by prenatal imaging. It may be difficult to counsel the parents because of uncertainty about the cause and the prognosis. When ventriculomegaly is detected on ultrasound screening there may be an underlying genetic disorder. Fetal MRI may demonstrate additional structural abnormalities that allow for more accurate counselling. Various CNS abnormalities may be found, such as dysgenesis of the corpus callosum, cerebellar hypoplasia, spinal cord defects, Chiari malformations, lissencephaly, and Dandy–Walker malformations. Those fetuses with additional CNS malformations and those with marked ventricular dilatation are less likely to progress to live delivery and to survive the neonatal period. In contrast fetuses with mild cerebral ventriculomegaly and no associated abnormality may show normal early postnatal development. Hydrocephalus This is ventriculomegaly caused by a disturbance of the normal flow pathway of cerebrospinal fluid. Cerebrospinal fluid is pro- duced by the choroid plexus in the lateral ventricles, from where it flows through the foramen of Munro into the third ventricle and then the fourth ventricle via the aqueduct of Sylvius. It leaves the ventricular system via small openings in the roof of the fourth ventricle, the foramina of Magendie and Luschka. From here the fluid flows in the subarachnoid space before being reabsorbed into the blood supply via arachnoid villi. Hydrocephalus is a rela- tively common problem, recently estimated to affect 11 in 10 000 infants. Two major forms of hydrocephalus are recognized: in commu- nicating hydrocephalus the ventricular pathways are clear and a failure of reabsorption by the arachnoid villi (after, for example, a bleed into the subarachnoid space) results in increased cerebro- spinal fluid volume. In obstructive or noncommunicating hydro- cephalus the blockage occurs at one of the ventricular levels, with expansion of the ventricular system above the block (Fig. 24.20.11). The major clinical sign that results is increasing head circumference following the ventricular enlargement, and this allows the distinc- tion from cases in which increased ventricular size resulting from cerebral atrophy is associated with a decreased head circumference. Fig. 24.20.11 Aqueduct stenosis in a boy aged one month with a bulging anterior fontanelle and increasing head circumference. Axial CT shows a gross dilatation of the third and lateral ventricles (the fourth ventricle is not shown, but was normal in size). Note the periventricular low density due to transependymal exudation of cerebrospinal fluid under pressure (arrow).

 Learning difficulties can result from both the damage associated with ventricular expansion and other abnormalities related to the underlying cause of the problem. Hydrocephalus may be acquired as the result of an

extrinsic event acting on a structurally normal brain. The most common cause of acquired hydrocephalus in infants is haemorrhage (e.g. intraventricular haemorrhage), most often as a result of pre- maturity. Other important causes include neoplasm and in- fection. Intrauterine infections with enterovirus, lymphocytic choriomeningitis, cytomegalovirus, and toxoplasmosis have all been associated with hydrocephalus. Hydrocephalus may be genetically determined, indeed there are many rare genetic disorders that can present with hydroceph- alus, or in which this may be a clinical feature. Stenosis of the aqueduct between the third and fourth ventricles can result from mutations in the cell adhesion molecule L1CAM. Hydrocephalus then occurs in association with hypoplasia of the corpus callosum, learning difficulties, spastic paraplegia, and adducted thumbs. Mutations in the X-linked gene L1CAM are found in as many as 75% of cases with a family history and 15% of apparently isolated cases. The abnormal genes that underlie congenital muscular dys- trophies may also cause hydrocephalus early in the clinical presen- tation of these disorders Most patients with neural tube defects have hydrocephalus, which may be multifactorial in origin. Hydrocephalus may be part of syndromes associated with intracranial cysts and also with megalencephaly (overgrowth of cerebral tissue). The devel- opmental abnormalities of the cerebellum in both the Dandy– Walker syndrome and the Arnold–Chiari malformation (see earlier) may also be associated with obstructive hydrocephalus. Although treatment via a ventriculoperitoneal shunt can relieve the obstruction, the other problems associated with these abnor- malities remain. Disorders of the developing brain caused
by external factors Alcohol Worldwide, alcohol is one of the most common preventable causes of learning difficulty and neurobehavioural disturbance in young children. Fetal alcohol syndrome may cause microcephaly, struc- tural anomalies of the brain such as partial or complete agenesis of the corpus callosum, cerebellar hypoplasia, and a dysmorphic appearance. These children may have impaired fine motor skills, sensorineural deafness, poor hand–eye coordination, and a poor tandem gait. Its prevalence depends on geographical location. An international survey in 1997 found that in the United States of America the prevalence per 1000 live births in Seattle was 2.8 and in Cleveland it was 4.6. The diagnosis of fetal alcohol syndrome can be made on the basis of the characteristic clinical features with or without confirmed maternal alcohol exposure. The term partial fetal alcohol syndrome can be used when there is a confirmed history of prenatal alcohol exposure without all the components of the full fetal alcohol syndrome. An alcohol-related neurodevelopmental disorder (fetal alcohol spectrum disorder) is also recognized that includes learning difficul- ties, poor impulse control, problems with social perception, deficits in higher level receptive and expressive language, poor capacity for abstraction, and difficulties with memory, attention, and judgement. The causes of these clinical features remain undefined, but animal studies show that alcohol is likely to affect multiple steps in CNS development including migration and neuronal survival. It is esti- mated that fetal alcohol spectrum disorder is one of the main causes of intellectual disability worldwide with a suggested prevalence as high as 2–5% of younger school children in the United States and Western Europe. Both regular and binge drinking can cause fetal alcohol syndrome and fetal alcohol spectrum disorder. Unlike many other teratogens, alcohol has harmful effects throughout pregnancy and it remains un- clear whether any amount of alcohol can be considered safe. Drugs of abuse Evidence is beginning to emerge that prenatal exposure to the stimulant drugs cocaine and methamphetamine may be particu- larly toxic to dopamine-rich basal ganglia regions of the brain, al- though the interpretation of such findings is limited by the problem of polysubstance abuse and the difficulty of obtaining precise ex- posure histories. Congenital infections Cytomegalovirus, herpes simplex virus, parvovirus, rubella, syphilis, toxoplasmosis, and varicella virus are all recognized as teratogens, with primary infection rather

than reinfection of the mother during pregnancy being more likely to result in congenital infection. Congenital infection should always be considered in the differential diagnosis of microcephaly. Intracranial calcifica- tion identified on cranial ultrasonography or CT (calcification is not picked up well by MRI) during the investigation of develop- mental delay or seizures suggests congenital infection, especially cytomegalovirus or toxoplasmosis. Ophthalmological assess- ment may show chorioretinitis (pigmentary retinopathy) or cata- ract, the former being characteristic of intrauterine infection by cytomegalovirus or toxoplasmosis. Sensorineural deafness is a common sequel to congenital infection with cytomegalovirus, ru- bella, and toxoplasmosis. There are several genetic disorders that mimic congenital infection with intracranial calcification evident on cranial imaging and sometimes with chorioretinal involvement. These include pseudo-TORCH syndrome due to biallelic mutation in OCLN or JAM3 and the pseudo-toxoplasmosis syndrome due to Aicardi–Goutières syndrome. Cytomegalovirus Although the risk of maternal–fetal transmission with primary cyto- megalovirus infection is as high as 40%, fewer than 10% of infants with intrauterine infection are symptomatic at birth. Of those, ap- proximately 90% have one or more of microcephaly, periventricular calcification, chorioretinitis, optic atrophy, and sensorineural deaf- ness. Of the 90% of infants who are asymptomatic at birth, approxi- mately 15% have sequelae including sensorineural deafness and/or developmental delay. Herpes simplex virus Intrauterine infection with herpes simplex virus is rare and neonatal infection acquired at the time of delivery is a more common cause of neurodisability than congenital infection. Congenitally affected in- fants may have microcephaly, chorioretinitis, and microphthalmos.

section 24 Neurological disorders 6364 Neonatal infection may cause meningitis and encephalitis with re- sulting neurological damage. The risks of perinatally acquired infec- tion may be reduced by appropriate obstetric intervention (such as delivery by caesarean section for women with active genital lesions resulting from herpes simplex virus) and by treatment of affected neonates with aciclovir. Rubella The classic triad of defects associated with congenital rubella syn- drome is sensorineural deafness, congenital heart disease, and eye abnormalities (retinopathy, cataracts, microphthalmos, and con- genital glaucoma). Microcephaly and developmental delay may also occur. The spectrum of defects in an individual child is determined by the stage of pregnancy at which intrauterine infection occurs. The risk of congenital infection is more than 90% if the mother has an infection in the first 10 weeks of the pregnancy and falls to zero be- yond 18 weeks. Toxoplasmosis The risk of intrauterine infection with toxoplasmosis increases with the stage of pregnancy at which the mother acquires her primary infection; however, the sequelae of intrauterine infection diminish with advancing gestation. Congenital toxoplasmosis syndrome in- cludes hydrocephalus, intracranial calcification, microcephaly, seiz- ures, and developmental delay. There may also be sensorineural deafness and chorioretinitis with visual impairment. Aicardi–Goutières syndrome is an important condition that can mimic con- genital toxoplasmosis and is caused by biallelic mutation in several genes resulting in a constitutive upregulation of type I interferon activity. Varicella Congenital varicella syndrome follows primary maternal varicella occurring at 1–20 weeks of gestation, but the risk of sequelae is small at around 2%. Cataracts and chorioretinitis may occur together with hypoplasia of the optic disc. Microcephaly and porencephaly have been described. Zika virus Zika virus disease is spread to people primarily through the bite of an infected Aedes species mosquito. This is the same mosquito that transmits dengue, chikungunya, and yellow fever. The most common symptoms of Zika infection are fever, rash, joint pain, and conjunctivitis (red eyes). The illness is usually mild with symptoms lasting for several days to a week. In 2016 there were numerous cases of microcephaly and other syndromes in

babies of mothers who were infected with Zika virus while pregnant. The virus can persist in the semen for some weeks and is transmissible through sexual contact. The cerebral palsies Although the aforementioned conditions are classified by aetiology or by anatomy, one important group of disorders is conventionally classified by their clinical presentation. These are the cerebral pal- sies, defined as a heterogeneous collection of nonprogressive dis- orders of movement and posture resulting from defects or lesions of the immature brain. Although the underlying causes of the cerebral palsy syndromes are by definition not progressive, the symptoms and signs of cerebral palsy do change with age (e.g. some children who are destined to have major problems with spasticity are ini- tially very hypotonic). In some cases, it can therefore be difficult to be sure whether or not a child with suspected cerebral palsy has a progressive underlying disorder. It may be necessary to allow the passage of time and children may be 3 or 4 years old before the diag- nosis of cerebral palsy can be made with confidence. Whatever the age at diagnosis, with the recent advances in imaging and genetics it is not satisfactory to label a child with neurological problems as having ‘cerebral palsy’ and go no further. It is important to deter- mine the type and distribution of the abnormality of motor control and evaluate other potential neurological problems, such as learning difficulties, epilepsy, and hearing or visual loss. Classification Patients may be classified according to the type of motor abnor- mality as follows: spastic, dyskinetic (dystonic or athetoid), ataxic, or hypotonic. The clinical picture is rarely clear cut and individuals may exhibit complex mixtures of motor disability. Patients are then subclassified according to the distribution of motor abnormality— in diplegia the legs are involved more than the arms, in quadriplegia all four limbs are involved, and in hemiplegia just one side of the body is involved. Epidemiology Overall, cerebral palsy rates since the mid-1950s have remained re- markably constant at about 2 to 2.5 per 1000 live births, although there have been some fluctuations with time. In 1970 the rate fell to 1.5 in Sweden, Western Australia, and Mersey (United Kingdom), rising again in the 1980s. In contrast, cerebral palsy rates stratified by birth weight do show marked changes with time. Most population- based registers have shown increases in rates in infants of very low birth weight (<1500 g) since the 1970s. For instance, in Mersey in the early 1970s the rate in infants of very low birth weight fluctuated around 10 per 1000 live births. In the late 1970s the rate increased sharply to about 50 per 1000 live births, presumably because more children of very low birth weight were surviving with neurological deficits. This increase was seen for all cerebral palsy types. However, to put the increasing cerebral palsy rates in survivors of very low birth weight in perspective, during this time an increasing propor- tion of patients were also surviving unimpaired. Although the risk of cerebral palsy is higher for preterm infants, the key observation is that most children with cerebral palsy are born at term. Overall rates have been determined mainly by the numbers of term infants born with cerebral palsy (and have remained fairly constant)However the contribution of prematurity and its complications to the prevalence of cerebral palsy has increased with time. Aetiology Genetic causes Genetic causes are clearly important because families have been reported in which spastic diplegia and quadriplegia (often with as- sociated learning difficulties) appear to be inherited in autosomal recessive, autosomal dominant, or X-linked recessive patterns. There can be a significant recurrence risk to future children, par- ticularly in populations where consanguineous marriage is rela- tively common. The highest risk of recurrence is in the category of

 children with ataxic cerebral palsy. However, there are many con- ditions that cause ataxia in children, making it important to search for an underlying cause before giving genetic advice, rather than to ‘lump’ this

group together and give an overall recurrence risk. Recent genetic studies of sporadic cerebral palsy cases using exome sequencing show that 14% of cases have likely causative single-gene mutations. Furthermore, babies with a pre-existing genetically de- termined neurodevelopmental disorder may be less resilient to ad- verse perinatal factors. Factors shown to increase the risk of cerebral palsy The rate of cerebral palsy among neonatal survivors born very pre- maturely is up to 30 times higher than among those born at term. Cerebral scans performed in newborn babies have shown that the strongest predictor of cerebral palsy in these infants is periventricular leucomalacia. This term is used for abnormal echolucency, often as- sociated with cystic change, which is found particularly in the white matter dorsolateral to the lateral ventricles (see Fig. 24.20.10a). Babies born small for their gestational age are also at increased risk of cerebral palsy and the risk increases with the degree of birth weight deficit. The underlying mechanism is not clear and it should be noted that most small-for-date infants do not have cerebral palsy. The prevalence of cerebral palsy is much higher in twins than in sin- gletons, particularly in those who survive after the other twin has died in utero and in monochorionic twins. The risk rises with the number of fetuses carried. When considering children born at term in developed countries, 10 risk factors for cerebral palsy have been identified in a systematic review: placental abnormalities, major and minor birth defects, low birthweight, meconium aspiration, instru- mental/emergency caesarean delivery, birth asphyxia (see next), neonatal seizures, respiratory distress syndrome, hypoglycaemia, and neonatal infections. Other possible causes include maternal iodine deficiency in early pregnancy which may cause endemic cretinism (spastic diplegia and deafness). Abnormal thyroid function in pregnancy may play a role in developed countries. Exposure to viral infections and to toxins during pregnancy may cause cerebral palsy—recognized examples are methylmercury, alcohol, and carbon monoxide poisoning. Finally, postnatal causes include CNS infections, accidental and nonaccidental head injuries, cerebrovascular accidents, and hypoxia (suffocation, near drowning). The role of birth asphyxia An important and controversial question that has significant medicolegal implications is the role of birth asphyxia in cerebral palsy. Although there may be some cases caused by intrapartum events that are preventable, these are likely to be rare. The best evidence for this comes from studies examining the impact of in- tensive electronic monitoring of the fetal heart rate during labour. These studies have found an increase in caesarean section rates and a reduced rate of neonatal seizures. There was, however, no impact on the rates of cerebral palsy. Epidemiological studies have shown that the origins of most cases of cerebral palsy are prior to labour. Currently, then, it is likely that many cases of cerebral palsy are wrongly attributed to an acute event during labour. In 1999, a con- sensus statement for the International Cerebral Palsy Task Force outlined a template for defining a causal relationship between acute intrapartum events and cerebral palsy. The statement emphasized the difficulty of retrospectively identifying the antenatal causes of cerebral palsy in the individual case and the nonspecific nature of the clinical signs that lead to the suspicion of fetal hypoxia in labour. Brain imaging in children with cerebral palsy Neuroimaging, especially MRI, plays an increasing role in the assess- ment of children with cerebral palsy, with abnormalities reported in almost 90% of affected children in published case series. The MRI findings vary according to the child’s gestational age at birth (term versus preterm) and according to the type of cerebral palsy. MRI abnormalities are most often seen in children with spastic and dyskinetic cerebral palsy and least often in those with the (relatively rare) ataxic type. The most common lesion in preterm infants is periventricular leucomalacia, which is necrosis of periventricular white matter in the watershed regions dorsal and lateral to the lateral ventricle (see Fig. 24.20.10a). This is said to be characteristic of damage in the early third trimester. Despite the fact that preterm children with cerebral palsy often have a pattern of injury

corresponding to the time of birth the scan findings do not provide exact information about the timing of the injury. In term infants, brain maldevelopment and grey matter lesions are more often seen than in preterm infants. Other findings are seen in infants born at or near term. These are infarcts in the arterial border zones in the parasagittal regions, leading to cortical and subcortical injury, bilateral lesions of the basal ganglia and the thalamus, areas of subcortical leucomalacia, and multicystic leucomalacia (replace- ment of the brain tissue by fluid-filled cysts). Basal ganglia/thalamus or bilateral cortico-subcortical lesions are highly associated with problems in the perinatal period. However, this conclusion cannot be drawn on the basis of the scan alone without other supporting clinical evidence. Children with hemiplegias are sometimes found to have periventricular leucomalacia, porencephalic cysts (see Fig. 24.20.10b), or cortical/subcortical lesions in the middle cerebral artery territory distribution (see Fig. 24.20.10c). The lesions tend to be unilateral, but bilateral lesions are also seen. Rarely they may have schizencephaly (see Fig. 24.20.10d), focal pachygyria, or focal heterotopia. Clinical approach to diagnosis and genetic counselling Assessing the nervous system in children History General The importance of the history cannot be overemphasized. Children may give a history themselves, but usually the parents or carers are an essential source of information, amplified by teachers, therapists, and other health professionals. Past history The pregnancy details are important. Significant events in the first trimester may include a threatened miscarriage, hyperemesis, or a viral infection, or the mother may have been taking medication. Later there may have been unsatisfactory fetal growth or reduced fetal movements. The perinatal history is relevant, including weeks

section 24 Neurological disorders 6366 of gestation at delivery, and details of labour, birth weight, and head circumference. In the neonatal period the infant may have required treatment for early hypoglycaemia, seizures, breathing, or feeding difficulties. A developmental history is essential—particular areas of concern in infants are lack of social response, absence of a social smile, poor fixing and following of the eyes, and lack of symmetrical organized limb movements. Later a characteristic pattern of delayed development may emerge (e.g. global delay is found in the most se- vere brain abnormalities or there may be mainly motor delay in the milder forms of cerebral palsy). Family and social history A three-generation family tree is required, with details of con- sanguinity, epilepsy, motor disorders, and learning disabilities. Considerable effort may be needed to obtain relevant facts—some families may not know about relatives with severe disability, per- haps because they are in institutions. Social factors are important in determining the environment in which the child grows up and they also determine the quality of care available for a child with sig- nificant disability. Examination Observation of spontaneous activity is essential. It may be helpful to use toys, bricks, beads for threading, paper, and crayons. The quality and symmetry of spontaneous movements should be noted and also any abnormal movements. If possible, it is best to assess muscle power by watching the child run, jump, and climb stairs. Fine motor function can be assessed while the child is drawing or threading beads. The conventional examination of the nervous system may be difficult in infants or young children (e.g. examination of the cranial nerves should be made a game by using a toy to observe eye move- ments and by encouraging the child to smile, whistle, close the jaw tight, stick out the tongue, and so on). The examiner may need to adapt the order of events or even come back later—a useful assess- ment cannot be made if an infant is deeply asleep or upset and crying. Developmental assessment may be undertaken using one of the standardized schedules, such as the Bailey Scales of Infant Development or the Denver Developmental Screening Test. Later the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and the Wechsler Intelligence Scale for Children (Revised)

(WISC- R) may be used, usually by a psychologist. Dysmorphic features are particularly relevant in the context of a suspected abnormality of the nervous system. There may be birth- marks (port-wine stain in Sturge–Weber syndrome or midline skin abnormalities such as hairy patches or dimples over the spine in neural tube defects). Other important skin abnormalities may ap- pear in infancy or early childhood. Examples are the pale ash-leaf patches, shagreen patches, and angiofibromas of the face (‘adenoma sebaceum’), which are found in tuberous sclerosis, or the café-au- lait patches and axillary freckling found in neurofibromatosis type I. A full eye examination is essential. In babies it may be necessary to dilate the eyes and come back to perform fundoscopy while the child is feeding (and therefore preoccupied). Indirect ophthalmos- copy by an experienced ophthalmologist is probably best. There may be abnormalities of the iris (such as colobomas in trisomy 13 and CHARGE syndrome, Lisch nodules in older children with neuro-fibromatosis type I, or Kayser–Fleischer rings in Wilson’s disease). Pale hypoplastic optic nerve heads are seen in septo-optic dysplasia and other congenital and acquired conditions. Significant retinal abnormalities include the chorioretinitis seen in congenital toxo- plasmosis, cytomegalovirus infections or KIF11 syndrome and the retinal ‘lacunae’ seen in Aicardi syndrome. Growth should be assessed by measuring weight, length (height), and head circumference, and plotting them on up-to-date growth charts. The head circumference should be related to the age of the child and to the other measurements. Changes with time may be significant, for example, after a severe perinatal insult the head cir- cumference may initially be in the normal range and then fall pro- gressively further below the expected centile line in the first few months of life. Investigations Cranial MRI is the cornerstone of investigations in children or adults with suspected disorders of CNS development. It is important to discuss the investigation with a neuroradiologist because spe- cial imaging sequences not normally performed may be required to visualize relevant abnormalities (e.g. subependymal nodules in tuberous sclerosis). Infants and young children may require sed-ation or anaesthesia for the procedure. CT does not provide the resolution of CNS structure obtained with MRI, but may be valuable if intracerebral calcification is suspected (as in tuberous sclerosis or cytomegalovirus infection). When routine antenatal ultrasound has shown abnormalities, there is increasing use of MRI scanning during pregnancy yielding images of the fetal brain before birth. Further investigations will depend on the specific diagnosis in question. Metabolic disorders can cause structural abnormalities in the developing CNS and routine investigations that may be appro- priate include plasma and urine amino acids, together with urine organic acids. In addition, further specific investigations may be in- dicated (e.g. in suspected Zellweger’s syndrome which is associated with pachygyria and is caused by abnormalities of very-long-chain fatty acid metabolism). Developmental anomalies of the CNS are seen in many chromo-somal disorders and so a genomic array is an important investiga- tion. These investigations may point to a diagnosis for which one or more genes have been shown to be responsible. A detailed clinical work-up is important to delineate the phenotype and facilitate inter- pretation of genetic investigations. Sequencing of individual genes is often an expensive and laborious investigation and is being rap- idly replaced by whole exome or whole genome sequencing studies. Establishing a genetic diagnosis enables confirmation of the clinical diagnosis and accurate assessment of risks for other family members following extended family testing. It may also enable more tailored clinical management and in future may be important for stratifica- tion of patients for therapy as response to different treatments may in some instances be dependent on the underlying molecular mech- anism of disease. Knowledge about the genetic basis of diseases is growing rap- idly but remains very incomplete. It is therefore valuable to take blood in order to extract and store DNA if no precise diagnosis can be reached, especially if life expectancy is short. Immediately after death

it may be appropriate to obtain a muscle or liver biopsy to help establish a diagnosis. Skin may be also obtained at this time to establish a fibroblast culture enabling further genetic and biochemical testing. Later other tissues can be frozen if a full post-mortem examination is performed. The ability to perform new tests many years after the death of the index case may be extremely valuable to other family members concerned about risks to their own offspring.

24.20 Developmental abnormalities of the central nervous system 6367 Risk assessment, genetic counselling,
and prenatal diagnosis Many families request genetic advice regarding a developmental disorder of the nervous system and they usually have four ques- tions in mind: • What is it? • Why did it happen? • Will it happen again? • What can be done to reduce the chance of it happening again, or to detect it if it does? If it is possible to make a specific genetic diagnosis (e.g. by identifying a pathogenic mutation), these questions can often be answered very accurately. In contrast, in the absence of a specific diagnosis, gen- etic advice is usually limited to empirical estimates. It is important to note that providing accurate genetic advice about developmental anomalies of the nervous system is a challenging task and that errors have far-reaching consequences for the families concerned. Referral for specialist advice by geneticists is strongly recommended. Prenatal diagnosis and termination of affected pregnancies is only one of a range of reproductive options open to parents at in- creased risk of having children with neurodevelopmental abnor- malities, but for many couples it is the option of choice. When a specific diagnosis has been made and a chromosomal anomaly, genetic mutation, or biochemical defect has been identified, it is usually possible to offer prenatal diagnosis by chorionic villus sam- pling at 11–12 weeks' gestation in a future pregnancy. Noninvasive prenatal testing for trisomy using free fetal DNA in the maternal serum is now widely available. Bespoke noninvasive single gene diagnosis is offered in some centres. Detailed ultrasonography may be helpful in other instances such as suspected neural tube de- fects. Ultrasonography has the potential to detect some structural anomalies but it does not provide information about key aspects of neurodevelopment, such as cognition, behaviour, vision, or hearing, and these limitations need to be discussed with parents. Although ultrasonography remains the initial investigation of choice for evaluating the fetus in utero, fast MRI is increasingly being used to image the fetal brain if there is concern about the ultrasound im- ages. MRI provides better images of CNS abnormalities and is not limited by interference from bony structures, so that posterior fossa abnormalities can be seen. In utero MRI is becoming increasingly valuable in antenatal counselling. For developmental disorders of the nervous system with proven disease-causing mutations and a high recurrence risk, preimplantation genetic diagnosis is available in some centres; up-to-date advice should be sought. For a condition following Mendelian inheritance, the option of donor gametes could be discussed. For conditions with a strong envir- onmental component, it is imperative that measures are taken to min- imize the risk of exposure in a future pregnancy, such as periconceptual supplementation with high-dose folate, which has been shown to re- duce the risk of recurrence of neural tube defects (see earlier). Acknowledgements We are very grateful to Dr Nagui Antoun (Addenbrooke's Hospital, Cambridge), Dr Fred Pickworth (Norfolk and Norwich Hospital), and Mr Paul Chamberlain (John Radcliffe Hospital, Oxford) for the scans shown in this chapter and for advice on their interpretation. Many thanks to Mr Michael Cafferkey (Senior Illustrator, Medical Photography and Illustration, Addenbrooke's Hospital, Cambridge) for producing Figs. 24.20.2 and 24.20.5. FURTHER READING Beeghly M, et al. (2010). Neurodevelopmental outcome of fetuses re- ferred for ventriculomegaly. Ultrasound Obstet Gynecol, 35, 405–16. Cooper GM, et al. (2011). A copy number variation morbidity map of developmental delay. Nat Genet, 43, 838–46. Deciphering Developmental Disorders Study (2017).

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