Malformations of the Brain

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Abstract. The purpose of this article is to provide a basic outline on which the reader can build a more elaborate and detailed knowledge of malformations of the brain. The first half of the article consists of a general approach to brain malformations; the second, the shortest possible description of the common brain malformations.

Key Words: Anencephaly; Brain malformation; Chiari II malformation; Cortical dysplasia; Dandy-Walker; Holoprosencephaly; Neuronal migration disorder.

GENERAL PRINCIPLES

Definition of a Malformation

"Congenital malformation" means that an organ is abnormal or malformed at the time of birth; the term implies no information about the cause of the malformation. "Primary malformation" is a term indicating that the genetic program or blueprint for formation is wrong, while "secondary malformation" or "disruption" indicates that a normal program has been interfered with by an extrinsic agent. (1)

Difficulties in Dealing with Malformations

The first difficulty in dealing with malformations of the brain is that within established morphologic diagnostic categories there is infinite variation. Each malformed brain should be regarded as unique and described in detail. There is a problem with cramming a case into a diagnostic category. Many of the terms we use such as anencephaly, holoprosencephaly, polymicrogyria, agyria, pachygyria, and Chiari II malformations come from the nineteenth century and do not correspond to the realities of causes and mechanisms (Table 1) as we are beginning to understand them; these terms should be regarded as descriptions only and not as diagnoses. An ideal complete diagnosis for a malformation of the brain includes not only the morphologic category, but also the cause and mechanism through which that cause operates. In our present state of knowledge, often only a morphological category can be assigned, or a descriptive diagnosis made.

The second difficulty in dealing with malformations is that with the exception of neuronal migration disorders, malformations are determined in the embryonic period which lasts from conception to 8 weeks (w) post-ovulation. It is necessary to visualize the early neural tube and brain as it exists during organogenesis in the embryo to understand malformations; it is difficult or impossible to extrapolate backwards from the adult brain. Descriptions

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<table>
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<tr>
<th>Malformation</th>
<th>Mechanism</th>
<th>Cause(s)</th>
<th>Timing</th>
<th>Comment</th>
<th>References</th>
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<tr>
<td>Split cord malformation: diplomyelia.</td>
<td>Persistence of primitive neurenteric canal.</td>
<td>Multifactorial is most common.</td>
<td>18 days p.o.</td>
<td>Persistence of neurenteric canal may interfere with neurulation.</td>
<td>2</td>
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<tr>
<td>Anencephaly.</td>
<td>Failure of neurulation due to abnormalities of mechanisms within the neural tube and/or failure of mesenchyme/mesoderm to grow properly. Some workers favor mesodermal failure as the major failure.</td>
<td>Multifactorial is most common. Can have other causes.</td>
<td>22–26 days p.o.</td>
<td>Preconceptional folate dietary supplementation reduces incidence of open NTD.</td>
<td>3, 4, 5, 6, 7, 8, 9</td>
</tr>
<tr>
<td>Encephalocele.</td>
<td>Failure of skull bones to close.</td>
<td>Multifactorial.</td>
<td>Occipital encephalocele between 3–7.8 w p.o.</td>
<td>A post-neuralization defect which occurs in many syndromes.</td>
<td>12, 13</td>
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<td>Holoprosencephaly.</td>
<td>Failure of prechordal plate to induce mediobasal portion of neural tube. Failure of mediobasal prosencephalon to grow due to excessive physiologic cell death or abnormal cell death.</td>
<td>Multiple (see text).</td>
<td>Failure of induction at 18 days p.o. for cyclops and up to 28 days failure of cerebral hemispheres to grow.</td>
<td>14, 15, 16</td>
<td></td>
</tr>
<tr>
<td>Migration Disorders/Cortical Dysplasias (many different).</td>
<td>Probably multiple, include abnormal neurons, abnormal migration, abnormal pial glial border (see text).</td>
<td>Probably established between 8–24 w gestation.</td>
<td>Probably each identifiable morphologic form will have a unique genetic cause and mechanism which differs from other morphologic forms.</td>
<td>17a</td>
<td></td>
</tr>
<tr>
<td>Agenesis of corpus callosum.</td>
<td>Probably multiple, includes absence of neurons giving rise to corpus callosum and absence of glial sling on which axons cross the midline.</td>
<td>Aicardi: X-linked dominant. Multiple others.</td>
<td>Reported in 70 syndromes.</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Dandy-Walker Syndrome.</td>
<td>Failure of cerebellar vermis to grow. ?Multifactorial. Isotretinoi.</td>
<td>By 7–8th w gestation.</td>
<td>Several other syndromes of cerebellar hypoplasia exist.</td>
<td>19, 20</td>
<td></td>
</tr>
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p.o. = post-ovulatory, w = week.
normalities of chromosomes 2p21 (2) and 7q36 (22). Abnormal genes involved in producing holoprosencephaly have been designated HPE 1–4 and are located respectively on chromosomes 21q22.3, 2p21, 7q36, and 18p (23). Holoprosencephaly can also be due to autosomal dominant inheritance with varying expressivity and autosomal recessive inheritance; it shows a weak association with maternal diabetes mellitus. There is nothing in the morphology of the brain to allow one to choose from these different causes of holoprosencephaly.

How to Deal With a Malformation

The autopsy of an older child or adult should afford no difficulties; however the reader unfamiliar with a fetal or perinatal autopsy is directed to Norman et al. (17b) and Dimmick and Kalousek (24) for a more detailed discussion of the type of autopsy that follows here. First, a detailed description of the fetus or infant is needed. External anomalies should be described; photographs may allow a geneticist to make the diagnosis of a syndrome at a later date. The brain should be described meticulously. Primary events should be differentiated from secondary events. For example, in alobar holoprosencephaly neither corpus callosum nor corticospinal tracts are present because the neurons that give rise to these tracts are absent. The absence of these tracts is not part of the primary abnormality, the failure of forebrain growth.

After the brain has been described and a morphologic category designated, a complete diagnosis should include the cause and mechanism by which the malformation occurred. The cause is important for genetic counseling of the parents of the affected infant. Causes of malformation fall into 5 groups: chromosomal anomalies, i.e. errors of chromosomal number or structure detectable by high resolution chromosome banding; single gene inheritance, i.e. autosomal recessive, autosomal dominant, and sex linked inheritance; teratogens, an external noxious agent that influences the development of the fetus; multifactorial, a combination of genetic and environmental factors; and “unknown,” the largest category.

Pregnancy history including an examination of the placenta may disclose pertinent information. Karyotyping of the fetus is necessary to establish the association with a chromosome abnormality; if a small deletion is responsible for the malformation, even high-resolution banding may be inadequate and a DNA probe may be required. Family history including examination of other family members may be necessary to establish single gene inheritance (autosomal dominant, recessive, or X-linked). A condition may be genetically determined even if only one family member is affected. If a malformation does not fit into a recognized diagnostic category, one cannot exclude the possibility of a new genetic condition. New mutations can occur and parental consanguinity increases the possibility of autosomal recessive inheritance; absence of parental consanguinity does not exclude it. The possibility that the condition is “private,” that is, unique to this particular family, is always worth considering. Genes causing specific malformations are being identified with increasing rapidity, but our knowledge of the mechanisms by which the malformations are established is incomplete.

A number of conditions exist which must be fulfilled before stating that a substance is a teratogen. Of these, probably the most important is that the agent must be present at the critical period in development, which, except for migration disorders, will be during the period of organogenesis, up to 60 days gestation (25, 26). One of the most common conceptual errors is to mistake association for causality. Two events that appear to be associated may have occurred together by coincidence. It is better to say the cause is unknown than to make an incorrect attribution.

New methods of diagnosis have altered the kind of material examined. Amniocentesis and karyotyping of cultured amniocytes made it possible to make an antenatal diagnosis of trisomy 21 and other chromosomal abnormalities. The polymerase chain reaction, fluorescent in situ hybridization, direct analysis of DNA performed on chorionic villus samples at a date earlier in pregnancy than can be done by amniocentesis have increased the number of chromosomal abnormalities and genetic abnormalities which can be detected before and after birth. Antenatal ultrasound examination of the mother has enabled us to detect gross structural defects, such as open neural tube defect, which are not associated with chromosomal abnormalities. Information about fetal abnormalities will often result in parents deciding to terminate their pregnancy. In our center it is mandatory to examine aborted fetuses to confirm the antenatal diagnosis. Saline abortions or dilatation of the cervix and evacuation of the uterus almost always make it impossible to confirm the diagnosis, in the former case due to severe maceration, in the latter due to fragmentation of the fetus, although the fragments can occasionally be informative. After prostaglandin-induced abortions the fetus may be sufficiently well-preserved to allow examination of the brain. It may be possible to make useful comparisons between the structure of the central nervous system in the fetus and cases of the same condition examined at term or later, which may give us an intimation of the mechanisms through which the cause is working.

FEATURES OF COMMON MALFORMATIONS

Anencephaly

In a term anencephalic infant (Fig. 1) the brain is reduced to a fibrovascular remnant, the area cerebrovascularis, in which there may be a few remnants of choroid plexus and occasional twists of glial tissue, ependyma, or
primitive neuroectodermal cells. The *area cerebrovasculosa* is what remains of exposed cerebral hemispheres (exencephaly) which have formed but have been destroyed during gestation. The eyes, which develop from the diencephalon, are present. Posteriorly, the occipital bones may have formed (macedrania); if not, the posterior portion of the posterior fossa and cervical spinal canal will be exposed (holoacrania). If the whole spine has failed to form, and the anterior aspect of the spinal canal is visible, this is called rachischisis. Rarely we have seen a remnant of spinal chord in the gutter of the open spinal canal; the dorsal root ganglia and peripheral nerves, which are derived from the neural crest, are always present. In anencephaly, by definition, there is no membrane covering the brain or remnants thereof (27), and calvarial bones are present, though small and deformed. Presence of a membrane covering the brain, with or without absence of all bones of the cranial vault, necessitates a diagnosis of aplasia cutis congenita or acalvaria. The only consistent abnormality in other viscera in anencephaly is hypoplasia of the adrenals due to destruction of the hypothalamus; it is usually possible to find a pituitary gland. Hypoplasia of the lungs is frequently attributed to lack of breathing movements in utero due to absence of the brainstem. The most common cause is multifactorial. Pre-conceptional supplementation of the mother's diet with folic acid reduces the incidence of neural tube defect (28). The mechanism by which folic acid affects this reduction is still unknown.

The cause of neural tube defect is unknown. The process of neurulation and closure is complex, requiring that the neural plate fold upward and over to fuse in the midline. It is not clear whether the primary defect lies in the neuroepithelium itself, the cytoskeleton, or in the mesoderm on either side of the neural tube. Müller and O'Rahilly (3) and Marin-Padilla (6) favor a primary mesodermal failure, that is, failure of the buttressing effect of the mesoderm on neural tube. More than one closure site exists in the head in mice and in humans, and Golden and Chernoff have recently reviewed the evidence sug-
gesting that there is more than one mechanism for closure of the anterior neural tube (8).

Open Meningomyelocele and Chiari II Malformation

In this malformation a tongue of inferior cerebellar vermis and an elongated medulla are both displaced into the cervical spinal canal (29) and are almost invariably associated with an open meningomyelocele (30). From an embryological point of view, the open neural tube defect probably antedates the posterior fossa malformation slightly. An open meningomyelocele, usually in the lumbosacral region, seems a prerequisite for the presence of the Chiari II malformation, for there are very few acceptable reports of the Chiari II malformation without an open defect (30). Closed defects such as meningocele are not associated with Chiari II malformation. From an embryological point of view the lumbosacral defect will occur slightly before formation of this posterior fossa and its contents. The best attempt to explain this malformation complex is that of McLone and Knepper (11), who suggested on the basis of experimental work that the same factor which led to failure of neurulation leads to failure of occlusion of the neuroccele, a “transitory normal embryological phenomenon.” This results in the failure of the ventricular system to grow, resulting in a small posterior fossa. When the cerebellar growth spurt occurs, the posterior fossa is too small to contain the cerebellum, so the contents of the fossa are squeezed out (11). There are difficulties with this explanation, but it is better than all those preceding it. Antenatal ultrasound examination has demonstrated that the hydrocephalus that almost always accompanies the Chiari II in a term infant does not develop until late in the first half of pregnancy, well after the neural tube defect and posterior fossa malformation have occurred; hydrocephalus is therefore a secondary manifestation in this malformation.

Examination of the open neural tube defect in the back shows a red, oozing, usually dome-shaped mass, the area medullovasculosa in which there may be some remnants of unneurulated spinal cord. It is this area which the neurosurgeon closes. The brainstem shows “beaking” of the tectum—that is, the four colliculi are compressed into a single mass which points caudally. There is kinking of the medulla. Microscopic examination may show considerable fibrosis and damage in the brainstem. The cerebral hemispheres may display a pattern of increased numbers of small gyri; microscopic section shows a six-layered cortex.

Conditions Associated with Neural Tube Defect

These include a heterogeneous group: cephaloceles, encephaloceles, meningoceles, split cord malformations, and malformations of structures derived from the caudal eminence. Encephaloceles occur in a number of sites; those most frequently seen by pathologists are occipital encephaloceles. In these, a variable portion of the occipital bone is missing and the defect is a sac which consists of epithelium and meninges-like tissue. Variable amounts of brain may be present in the sac. If there is no brain in the sac, the lesion is a cephalocele; if there is brain in the sac, it is an encephalocele. More than half of the cerebral hemispheres, always unequal amounts from each hemisphere, and portions of the brainstem and cerebellum may be contained in the sac. Abnormalities of the brain in the sac should be considered deformations and disruptions. There are approximately 40 conditions (13) in which an encephalocele occurs. The Meckel-Gruber syndrome is transmitted as an autosomal recessive and is associated with cystic dysplasia of the kidney and hepatic ductal-plate malformation. Holoprosencephaly is fairly common in the Meckel-Gruber syndrome (31). The amnion rupture sequence (amniotic band syndrome, amniotic adhesion sequence, limb-body-wall complex) (32) may have an encephalocele, anencephaly (Fig. 2) or exencephaly, and occasionally aqueduct stenosis. There may be amputations of the digits due to amniotic bands, or defects of the anterior abdominal wall. It is considered a non-recurring sporadic condition, so it is important to recognize for the purposes of genetic counselling.

Cerebral Hemisphere

In many chromosomal abnormalities and dysgenetic or dysmorphic syndromes, the brain may be smaller than normal and the gyral pattern abnormal. The centrum ovale, the region of the hemisphere where the corpus callosum and internal capsule intersect, may be reduced in size, and the corpus callosum may be thinner than that in an age-matched normal control, but not small in relation to the brain itself. The lateral ventricles may seem large in relation to the brain, but in a malformed brain this means neither obstruction of cerebrospinal fluid (CSF) flow nor destruction of cerebral parenchyma, but failure of the cerebral mantle to grow. Colpocephaly refers to enlargement of the posterior portions of the ventricle. In the fetus of 8 w the lateral ventricles are initially large and the cerebral mantle very thin. Both ventricles and cerebral mantle grow, but the growth of the mantle outstrips the increase in ventricular size gradually until the adult relationship of a thick mantle surrounding small ventricles is achieved. Since enlarged ventricles are a feature of many, if not most severe malformations, and can be particularly marked in the fetus, enlarged ventricles in a fetus cannot be equated to obstruction of CSF flow. Cases of true fetal hydrocephalus, a term which should be restricted to cases with obstructed CSF flow, do occur, but are infrequent and the cause usually cannot be found.

Holoprosencephaly

In holoprosencephaly the mediobasal prosencephalon, which gives rise to the frontal portion of the cerebral
hemispheres, fails to grow. In cyclopia, there is a single central eye and the condition is virtually always associated with severe forms of holoprosencephaly; it should be regarded as a failure in lateralization of structures initially represented in a median position. The holosphere is a cup- or bowl-shaped mass containing a single ventricle. At the base the basal ganglia may or may not be evident; frequently they are small and fused into a single mass. The thalami are fused and covered by an astroglial crust. The corpus callosum and corticospinal tracts are absent because the neurons which give rise to these tracts are absent. The olfactory tract and bulb are absent. The cerebellum and brainstem are usually normal. The malformation is sometimes graded into alobar (Fig. 3), semilobar, and lobar depending on the degree of development of the cerebral hemispheres. The cerebral cortex should continue across the midline for a diagnosis of lobar holoprosencephaly. The microscopic appearance of the cortex is abnormal, but the abnormality of the cortex lessens as the gross appearance of the brain becomes more normal. The brain abnormality is almost always associated with a facial abnormality such as anophthalmia, cyclopia, synophthalmia, ethmocephaly, ceboccephaly, and other less severe facial dysmorphisms (33).

Neuronal Migration Disorders and Cortical Dysplasias

Historically the diagnosis of neuronal migration disorder was made at autopsy in a case where the cerebral cortex showed a global disorder, whereas cortical dysplasia was a diagnosis made on the basis of cytologic abnormalities in portions of cerebral hemispheres resected for the control of seizures. The distinction between neuronal migration disorders and cortical dysplasias is arbitrary. There is no guarantee that the neurons in neuronal migration disorders are normal; in cortical dysplasias cortical lamination is usually abnormal. Some workers use the terms "neuronal migration disorder" and "cortical dysplasia" interchangeably. The appearance of normal cerebral cortex depends on a number of conditions: generation of young neurons at the ventricular surface (young neurons are post-mitotic as soon as they are
formed); normal migration of young neurons away from the generative zone into the cortex on both radial glia (34), and tangentially, termination of migration in the cortex for which an intact, pial-glial border of the cerebral hemisphere is only one requirement (35); growth of axons into the cortex; normal intracortical growth of neurons and glia, and formation of normal synapses (a neuron which fails to make a synapse with another neuron will die, histogenetic, programmed cell death, or apoptosis). Death of neurons due to either intrinsic abnormal or extrinsic causes en route to cortex or after they have reached it will also result in abnormalities in the cortex, usually polymicrogyria. In cases where the cortical lesion is not due to a destructive event but to a genetic abnormality, frequently there will be associated abnormalities in the cerebral hemispheres such as heterotopic grey matter (Fig. 4) between ependyma and cerebral cortex, abnormalities of cerebellar cortex, and abnormal dentate and inferior olivary nuclei. Although methods of imaging, particularly nuclear magnetic resonance imaging, are extending our knowledge of migration disorders and dysplasias, it should be remembered that definitive diagnosis must always be made pathologically, not by an imaging study. I believe that the rational way of classifying migration disorders and cortical dysplasias is by cause and mechanisms, as more than one morphologic abnormality can occur in a single brain. In both the Walker-Warburg syndrome and the Zellweger syndrome the gross appearance of the cerebral hemisphere is a mixture of pachgyria (overly-broad gyri) and polymicrogyria (excessively small gyri) (36). Also, particularly in genetically determined cases, the cause and mechanism will almost certainly be unique for each disorder.

Deletion of a small portion of chromosome 17p13.3
cells, and histiocytes spread throughout the brain, is due to absence of peroxisomes. The gene for a peroxisomal membrane protein with a relative molecular mass of 70KDa has been localized to chromosome 1p21p22 (39), and a subset of Zellweger cases may be due to abnormalities of the peroxisomal protein. In Zellweger syndrome there is an excess of long chain fatty acids due to lack of peroxisomal function; it is not clear how this causes the observed morphological abnormalities in the cortex.

There is a third group of migration disorders due to autosomal recessive inheritance. The Galloway-Mowat (40, 41) syndrome and the Neu-Laxova (35) syndrome have now been reported in 20 or more cases and are the most common. In the Galloway-Mowat syndrome there is a subpial glial crust containing neurons (40); the abnormality is probably due to failure of the pial-glial border to form properly. The brain abnormality is associated with the congenital nephrotic syndrome. The Neu-Laxova syndrome (42) is probably due to loss of cells in the ventricular zone in the first half of pregnancy and in the cerebral cortex in the second half of pregnancy.

A syndrome described solely in females and named for the appearance of a “double cortex” in neuroimaging consists of mental retardation, epilepsy, and behavioral problems; it has not been studied pathologically (43). Many other syndromes have been reported and pathologically confirmed having occurred less frequently, sometimes in only one individual or in one family. These cases can be called “private,” as they are genetic abnormalities seen only in one person or family. In my experience, brains with migration disorders which cannot be assigned to one of the common groups already noted are morphologically unique, and the geneticist must be informed that the cause is unknown but that autosomal recessive inheritance or a new mutation cannot be excluded.

In polymicrogyria (Fig. 6) the gross surface of the brain is finely cobbled, or the gyri are too small, too abundant, and shallow. Viewed microscopically the cerebral cortex is festooned, can vary from 1 to 4 layers, and often may contain an acellular layer; the patterns vary from case to case, even within a single case. Polymicrogyria occurs at the edge of destructive lesions, which may or may not be cavititated. In addition it occurs in cytomegalovirus infection without obvious destruction, and in a miscellany of conditions including Aicardi syndrome and Zellweger syndrome where the cause is unknown.

In cortical dysplasia individual neurons and glia are morphologically abnormal and frequently enlarged (44). In one series almost half the cases were considered to be a forme fruste of tuberous sclerosis (45). Generalized cortical dysplasia, in which abnormal neurons were found throughout the cortex of microencephalic brains, has been described (46). The precise mechanism for these groups...
of abnormalities has not been described. Two forms of tuberous sclerosis have been found. TSC1 has been mapped to 9q32-934. TSC2 has been mapped to 16q13.3, the gene cloned, and it may be that very soon the mechanism by which the abnormalities in tuberous sclerosis are determined will be found.

Crossing the Midline

Much of the formation of the brain has to do with "wiring," that is, the connecting of one group of neurons to another. For this to occur the neuron must be intact and capable of growing out an axon to the correct target, there forming a synapse or neuro-muscular junction from which trophic substances are transmitted back to the neuron. If a neuron fails to make a synapse, it will die (histogenetic, physiologic, or programmed cell death). Three errors of midline crossing are known. There are probably other conditions of miswiring which we have not recognized. Axons of the corpus callosum may fail to cross the midline; in albinos axons of the medial temporal retinal neurons which should remain ipsilateral make an abnormal crossing at the optic chiasm and go to the contralateral side, and axons of the corticospinal tract may fail to decussate in the medulla and do so at a lower level. In agenesis of the corpus callosum, as well as the general requirement for neurons, axon, and target to be intact, the glial sling on which the axons cross the midline must be intact (18). Isolated agenesis of the corpus callosum can occur without overt clinical symptoms. When clinical symptoms are present they are due to the other abnormalities in the brain. In agenesis of the corpus callosum the ventricles have a "Viking helmet" configuration on imaging studies. The cingulate gyrus fails to form and the gyri on the medial surface of the brain are radially arranged and curl into the ventricle. An extra bundle of fibers, Probst's bundle, is found. The prototype syndrome for agenesis of the corpus callosum is Aicardi syndrome, which is probably an X-linked dominant and is lethal in males. Choreoretinitis and infantile spasms are the 2 other features necessary for a diagnosis of Aicardi syndrome. In 3 of our 4 cases of Aicardi syndrome a small or partial corpus callosum was present; in addition, heterotopic grey matter at the ventricular surface and polymicrogyria are usually found.

Agenesis of the corpus callosum is found with variable frequency in some 70 syndromes including a group of metabolic diseases, so it cannot be regarded as a highly specific finding. In BALB mice with agenesis of the corpus callosum the inheritance of the defect is polygenic, with 2 autosomal loci involved (18). Alterations in the maternal environment will influence the number of fetal mice affected, and this may be an example of "threshold effect." This genetic background may in part explain why the defect is so variable in humans.

Malformations of the Cerebellum

A number of syndromes of aplasia of the cerebellar vermis exist. In the Dandy-Walker syndrome the primary abnormality is vermal hypo- or aplasia with cystic dilatation of the fourth ventricle; an elevated tentorium, large posterior fossa, and hydrocephalus are secondary abnormalities. The condition is sporadic, with only a few familial cases reported. Most seem to be of multifactorial origin, although some cases are associated with treatment of the mother's acne with isotretinoin during pregnancy (47). A rare malformation is rhombencephalosynapsis in which vermal agenesis results in fusion of the dentate nucleus across the midline.

A number of heterotopias and heterotaxias of primitive and mature neurons occur in the cerebellum. These are probably not of great importance. Huge masses of primitive cells mixed with neurons can occur in trisomy 13. In migration disorders other abnormalities can occur: in Zellweger syndrome Purkinje cells are misplaced, in Walker-Warburg syndrome and FCMD the cerebellar cortex is considerably scrambled (cerebellar polymicrogyria).

Destructive and Degenerative Lesions

Since the term "congenital malformation" means only that an organ is abnormal at birth, destructive and degenerative lesions are technically congenital malformations. The destructive lesions are usually easily recognizable as such. Porencephaly, as originally defined, was a cyst which went from ventricle to arachnoid; now it is loosely defined as any cyst in an infant's brain. Hydranencephaly is a combination of bilateral porencephaly and aqueduct stenosis. The basic difference between porencephaly and hydranencephaly is the degree of destruction of the cerebral hemispheres. These lesions can
be caused by a number of different destructive agents: an hypoxic-ischemic insult, viral infection, or primary hemorrhage due to maternal ingestion of anticoagulants or maternal platelet antibodies. Usually it is not possible to identify the cause from the morphology of the brain. In both of these conditions, the gyri radiate into the defect if the lesion has occurred before the gyral pattern is complete. Uni- or bilateral scars that usually appear in the insular area (referred to as schizencephaly, a term used by radiologists) are frequently bordered by polymicrogyria, as are the cavitated defects. Multicystic encephalomalacia, which denotes multiple cavities in the brain with a gyral pattern that is normal or nearly normal usually occurs in the last weeks of gestation or just after birth. Other destructive lesions are the fetal brain disruption sequence, aprosencephaly/acephalencephaly, and septo-optic dysplasia (de Morsier syndrome).

Degenerations of the grey matter can occur even before birth. They can involve the cerebral cortex, thalamus, cerebellar cortex, pontine nuclei, and inferior olivary nuclei in any combination, with differing degrees of involvement of the various anatomical structures. The pathology is non-specific, usually neuronal loss with or without microglial shrubs or stars, and gliosis. Some of these are transmitted as autosomal recessive traits, but unfortunately the only way of recognizing this is by the birth of a second affected child in a family. Currently the cause and mechanism by which these degenerations occur is unknown.

REFERENCES
MALFORMATIONS OF THE BRAIN


Related Reading


