Developmental and Congenital Disorders

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This section reviews normal infant and childhood development as well as abnormalities seen with common genetic and structural anomalies.

Normal Developmental Milestones

Normal developmental milestones are outlined in Table 1. Well-child examinations during infancy and early childhood provide an opportunity to assess for delayed development. The Ages & Stages Questionnaire (ASQ) and Modified Checklist for Autism in Toddlers, Revised (M-CHAT-R) are commonly used validated screening forms. Blood should be evaluated for iron deficiency and lead poisoning when developmental delay is diagnosed, as these are common and treatable conditions. The general physical examination can often aid diagnosis; dysmorphic features suggest a genetic etiology, specific birthmarks may indicate a neurocutaneous disorder, and hepatosplenomegaly raises concern for a metabolic disorder.

**Table 1. Normal Developmental Milestones**

<table>
<thead>
<tr>
<th>Age</th>
<th>Gross Motor</th>
<th>Fine Motor</th>
<th>Language</th>
<th>Social</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Months</td>
<td>Holds head up</td>
<td>Grasps rattle</td>
<td>Coos</td>
<td>Reciprocal smile</td>
</tr>
<tr>
<td>4 Months</td>
<td>Rolls front to back</td>
<td>Reaches for toys</td>
<td>Vocalizes when alone</td>
<td>Spontaneous smile</td>
</tr>
</tbody>
</table>

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### Microcephaly and Macrocephaly

Microcephaly is defined as occipitofrontal circumference of more than two standard deviations below the mean while macrocephaly is defined as occipitofrontal circumference of more than two standard deviations above the mean. Table 2 outlines specific etiologies.

**Table 2. Causes of Microcephaly and Macrocephaly**

<table>
<thead>
<tr>
<th>Microcephaly</th>
<th>Macrocephaly</th>
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</thead>
<tbody>
<tr>
<td><strong>Genetic causes</strong></td>
<td></td>
</tr>
<tr>
<td>• Trisomies</td>
<td></td>
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<tr>
<td>• X-linked microcephaly</td>
<td></td>
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<tr>
<td><strong>Neuroanatomic abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>• Neural tube defects</td>
<td></td>
</tr>
<tr>
<td>• Holoprosencephaly</td>
<td></td>
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<tr>
<td>• Neuronal migration disorders</td>
<td></td>
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<tr>
<td>• Perinatal ischemia</td>
<td></td>
</tr>
<tr>
<td><strong>Increased CSF</strong></td>
<td></td>
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<tr>
<td>• Hydrocephalus</td>
<td></td>
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<tr>
<td>• Benign enlargement of the subarachnoid space</td>
<td></td>
</tr>
<tr>
<td><strong>Increased brain matter</strong></td>
<td></td>
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<tr>
<td>• Anatomic megalencephaly</td>
<td></td>
</tr>
<tr>
<td>o Benign familial megalencephaly</td>
<td></td>
</tr>
<tr>
<td>o Neurocutaneous disorders</td>
<td></td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>Environmental factors</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>• Phenylketonuria</td>
<td>• TORCH infections</td>
</tr>
<tr>
<td>• Neuronal ceroid lipofuscinosis</td>
<td>• In utero toxin exposure</td>
</tr>
<tr>
<td>• Citrullinemia</td>
<td></td>
</tr>
<tr>
<td>• Maternal diabetes mellitus</td>
<td></td>
</tr>
</tbody>
</table>

| Common Genetic Conditions              |

A genetic workup is typically initiated when dysmorphic features accompany developmental delay or if the etiology of delay is unclear. Karyotype analysis can detect aneuploidy, including monosomies and trisomies such as trisomy 21 (Down syndrome). Chromosomal microarray is more sensitive for smaller duplications or deletions.

Diagnosis of Down syndrome is often made with prenatal testing. Typical dysmorphic features include upslanting palpebral fissures, epicanthic folds, and brachycephaly. Diffuse hypotonia leads to delayed motor milestones, with an average walking age of 26 months. Most children with Down syndrome have mild to moderate intellectual disability.

Fragile X syndrome is the most common inherited disorder of intellectual disability. It is caused by trinucleotide repeats (CGG) in the **FMR1** gene on the X chromosome and can affect both girls and boys, although boys are more severely affected.
overall. A full mutation has over 200 repeats. Dysmorphic features include a long narrow face, large ears, macrocephaly, and testicular enlargement. The average age of walking is 20 months and about 10% of children are nonverbal. Intellectual disability is typically moderate and many affected individuals have behaviors consistent with attention deficit hyperactivity disorder. Seizures are present in 10% of cases.

Rett syndrome is another inherited X-linked genetic disorder of neurodevelopment that exclusively affects girls. Almost all cases are due to de novo mutations in the MECP2 gene, although Rett-like syndromes have been associated with CDLK5 and FOXG1 mutations. Clinical manifestations include microcephaly, developmental regression, midline hand stereotypies, autistic behaviors, and seizures. The prevalence of epilepsy increases with age and reaches almost 90% by adulthood.

Prader-Willi syndrome, due to paternal loss of 15q11-13, is known as the most common syndromic cause of hyperphagia and obesity in later childhood. However, in infancy it is characterized by hypotonia and feeding difficulties due to poor suck. There is often delayed motor development but no regression. Mild to moderate cognitive impairment is common. Characteristic dysmorphic features, including almond-shaped eyes, narrowed forehead, down-turned mouth, and thin upper lip can hint toward diagnosis. Diagnosis is made by methylation analysis, and confirmed by fluorescence in situ hybridization (FISH) or chromosomal microarray (CMA) if the methylation screen is abnormal.

Angelman syndrome is caused by maternal loss of 15q11-13 and is characterized by intellectual disability, epilepsy (80%), microcephaly, and a happy demeanor. There is often hyperactivity with stereotypies and fascination with water. As with Prader-Willi
syndrome, the diagnosis is made by methylation analysis and confirmed by FISH or CMA.

Autism spectrum disorder is a prevalent neurodevelopmental disorder of social communication and restricted interests. The 2011-2012 National Survey of Children’s Health estimated a prevalence of 1 in 50 children. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, criteria require all of the following symptoms for diagnosis:

- Persistent deficits in social communication and social interaction across multiple contexts.
- Restricted, repetitive patterns of behavior, interests, or activities.
- Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
- Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
- These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

The diagnosis of autism spectrum disorder is made clinically and supported by validated assessment tools. Once the diagnosis is established, chromosomal microarray
and fragile X testing is recommended for evaluation of underlying genetic causes.

Neuroimaging is not recommended unless a history of seizures, microcephaly, or developmental regression is present. Management involves aggressive behavioral therapy as well as school support.

**Primary Brain Lesions**

Most primary structural brain anomalies occur during fetal development. The first milestone of central nervous system development is neural tube closure, which occurs around 3 to 4 weeks postconception. Failure of neural tube closure can lead to spinal cord and brain anomalies, including anencephaly, encephalocele, and spina bifida (Table 3). Risk factors for neural tube defects include low maternal folate levels and exposure to antiepileptic drugs such as valproic acid, carbamazepine, phenytoin, and phenobarbital. Prenatal vitamins with folate supplementation, taken early in pregnancy, significantly reduce the risk.

**Table 3. Definition and Characteristics of Neural Tube Defects**

<table>
<thead>
<tr>
<th>Condition/Location of Closure Defect</th>
<th>Definition</th>
<th>Clinical Features</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly/rostral</td>
<td>Absent forebrain</td>
<td>Lethal; preserved brainstem activity, but unconscious</td>
<td>Elevated prenatal α-fetoprotein; prenatal ultrasound</td>
<td>Intensive vs palliative support; consider organ donation</td>
</tr>
<tr>
<td>Encephalocele/rostral</td>
<td>Protrusion of brain and/or meninges through skull defect</td>
<td>Occipital protrusion of brain and meninges; developmental delay and epilepsy</td>
<td>Elevated prenatal α-fetoprotein; prenatal ultrasound; MRI</td>
<td>Surgical correction</td>
</tr>
<tr>
<td>Meningomyelocele/caudal</td>
<td>Protrusion of spinal cord and meninges through vertebral column cleft</td>
<td>Lower extremity weakness and sensory loss; often associated</td>
<td>Elevated prenatal α-fetoprotein;</td>
<td>Surgical closure; treatment of hydrocephalus if indicated</td>
</tr>
</tbody>
</table>
Spina bifida occulta/caudal  | Failure of vertebral body fusion; unexposed neural tissue with skin intact | Often asymptomatic; presents after infancy (mean age 2 years old); tethered cord; bladder dysfunction | Ultrasound (newborns) or spine MRI in older childrens | Surgery if indicated

**Holoprosencephaly**

Around the fifth week after conception, the primordial brain divides into two halves.

Failure of this process results in holoprosencephaly. The three types of holoprosencephaly are lobar, semilobar, and alobar. Lobar holoprosencephaly is the least severe, with formed right and left ventricles and two hemispheres with continuity across the frontal cortex. Alobar is the most severe, with a single large ventricle. Midline facial defects, such as cleft lip/palate, single central incisor, hypotelorism, and even cyclopia are common.

*SHH* (sonic hedgehog), *SIX3* (sine oculis homeobox), and *TGIF* (transforming growth factor-beta-induced factor) are genes that have been associated with holoprosencephaly, although environmental factors are thought to play a role, as well. Maternal diabetes mellitus; toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex (TORCH) infections; and alcohol abuse during pregnancy have been implicated.

**Neuronal Migration Disorders**

Neuroblasts migrate via radial glial cells to form the cortex during the second trimester of pregnancy. Lissencephaly is a lack of gyri and sulci and results in a smooth brain surface due to failure of neuronal migration. It is often associated with mutations in the *LIS1* gene. Other disorders of neuronal migration include pachygyria (large gyri),
polymicrogyria (multiple small gyri), gray matter heterotopia, and focal cortical
dysplasia. In a study of 109 children with neurodevelopmental lesions, heterotopia was
the most common neuronal migration defect reported. Epilepsy, often intractable, and
developmental delay are the most common clinical manifestations.

**Chiari Malformations**

Chiari type I malformation (CMI) is defined as downward displacement of the cerebellar
tonsils below the foramen magnum in the absence of edema or mass effect. Generally,
tonsils that are 5 mm below the foramen magnum qualify for diagnosis. CMI is often
asymptomatic and found incidentally on head imaging, and because of this a good
estimate of the prevalence of this malformation is not available. Previous estimates
indicate a prevalence of 0.1% to 0.5%. Up to 80% of cases are associated with
syringomyelia. When symptomatic, clinical manifestations are due to brainstem
compression or increased intracranial pressure. Common symptoms include headache
with Valsalva maneuver, lower cranial neuropathies such as hoarseness and dysarthria,
vertigo, and signs of increased intracranial pressure due to hydrocephalus. Surgical
decompression and shunt placement are indicated for symptomatic patients.

Chiari type II malformation (CMII), also known as Arnold-Chiari malformation,
is more severe and involves extension of the cerebellar vermis and tonsils as well as
brainstem into the foramen magnum, with resulting hydrocephalus. It is usually
accompanied by myelomeningocele. MRI can reveal a “beaked” quadrigeminal plate,
kinking of the medullary spinal cord junction, and cerebellar dysplasia. CMII is typically
diagnosed on prenatal ultrasound.
Chiari type III malformation is rare and most severe. It is characterized by downward displacement of the medulla along with high cervical or occipital encephalocele that may contain cerebellum or occipital lobe tissue. Infants with this malformation have a high mortality rate and severe neurologic deficits.

**Dandy Walker Malformation**

Dandy-Walker malformation is a neurodevelopmental disorder of the hindbrain. The malformation occurs around the sixth or seventh postmenstrual week, resulting in characteristic lesions including an enlarged fourth ventricle, large posterior fossa cyst, and hypoplasia or agenesis of the cerebellar vermis. Seventy-five percent of patients have associated hydrocephalus.

**Secondary Brain Lesions**

**Germinal Matrix Hemorrhage**

The germinal matrix is a highly vascularized structure that is prone to rupture in premature infants born at less than 32 weeks’ gestation. Germinal matrix hemorrhages lead to intraventricular hemorrhage (IVH) and are the most common cause of brain injury in newborns. Severity is graded based on cranial ultrasound findings.

- Grade I IVH is limited to hemorrhage in the germinal matrix.
- Grade II IVH is hemorrhage in 10% to 50% of the lateral ventricle, while grade III IVH is more than 50% filling of the ventricle, typically with ventricle enlargement.
- Grade IV IVH is now referred to as periventricular hemorrhagic infarction (PVHI) and involves IVH with parenchymal hemorrhage.

Mortality is about 20% in severe cases (grade III and PVHI). Survivors are at risk for hydrocephalus and cerebral palsy. A large prospective study showed that cerebral
palsy was diagnosed at 5 years of age in 8% of survivors with grade I IVH, 11% with grade II IVH, 19% with grade III IVH, and 50% in PVHI.

**Periventricular Leukomalacia**

Periventricular leukomalacia typically develops in premature infants but can develop in utero or in term infants. The etiology is typically ischemia or infection resulting in bilateral periventricular focal necrosis. Cystic lesions are typically seen on follow-up imaging. Ultrasound is an easy and inexpensive screening test in newborns, but MRI is more sensitive. Periventricular leukomalacia is a common cause of cerebral palsy, particularly spastic diplegia, and intellectual impairment.

**Porencephaly**

In utero, cerebral ischemic events that occur during the first 6 months of fetal life can cause cystic cavities lined by white matter, termed *porencephalic cysts*. The cysts are lined by white matter, as opposed to schizencephaly, in which the fluid-filled intracerebral clefts are lined by gray matter. Porencephalic cysts can be differentiated from arachnoid cysts, since they are intra-axial while arachnoid cysts are extra-axial. The outcome for individuals with porencephaly ranges from asymptomatic to cerebral palsy with intellectual disability.

**TORCH Infections**

The TORCH acronym refers to congenital infections acquired in utero, specifically toxoplasmosis, other infections (eg, syphilis), rubella, cytomegalovirus infection, and herpes simplex. Table 4 lists the common neurologic manifestations associated with each infection.

**Table 4. Neurologic Complications of TORCH Infections**
<table>
<thead>
<tr>
<th>Organism</th>
<th>Neurologic Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasmosis</td>
<td>Chorioretinitis, hydrocephalus, intracranial calcifications</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Chronic meningovascular syphilis; acute syphilitic leptomeningitis; seizures later in life</td>
</tr>
<tr>
<td>Rubella</td>
<td>Sensorineural deafness</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Microcephaly, intracranial calcifications, sensorineural hearing loss, chorioretinitis, and seizures</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Encephalitis; see the section Infectious Disease for details</td>
</tr>
</tbody>
</table>

**Neurocutaneous Disorders**

**Neurofibromatosis**

Neurofibromatosis (NF) type 1 (NF1) is an autosomal dominant disease caused by mutations in the \( NF1 \) gene on chromosome 17.q11.2. Fifty percent of cases are familial, while de novo mutations account for the other half. Diagnosis can be made clinically, but genetic testing is also available for atypical cases. Clinical diagnosis requires at least two of the following:

- Six or more café-au-lait macules:
  - More than 5 mm in greatest diameter in prepubertal children
  - More than 15 mm in greatest diameter in postpubertal individuals
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Freckling in the axillary or inguinal regions
- Optic glioma
- Two or more iris hamartomas (Lisch nodules)
- Distinctive bony lesion, such as sphenoid dysplasia, or thinning of the long bone cortex with or without pseudarthrosis
A first-degree relative (parent, sibling, or offspring) with NF1 based on the above criteria

Other associated features include increased risk of seizures, macrocephaly, and cognitive and learning disabilities.

Neurofibromatosis type 2 (NF2) is also inherited in an autosomal dominant pattern. The NF2 gene is located on chromosome 22 and encodes the tumor suppressor protein, merlin. Tumors are more common than skin lesions. Clinical diagnostic criteria were updated in 2017 to account for LZTR1-related schwannomatosis (Table 5).

**Table 5. Current and Revised Manchester Criteria for Neurofibromatosis Type 2 (NF2)**

<table>
<thead>
<tr>
<th>1. Bilateral vestibular schwannomas &lt;70&lt;sup&gt;a&lt;/sup&gt; or</th>
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<tbody>
<tr>
<td>2. FDR family history of NF2 and unilateral VS &lt;70&lt;sup&gt;a&lt;/sup&gt; or</td>
</tr>
<tr>
<td>3. FDR family history of NF2 or unilateral VS and two of meningioma, cataract, glioma, neurofibroma, schwannoma, cerebral calcification (if UVS + ≥2 nonintradermal schwannomas need negative LZTR1 test&lt;sup&gt;a&lt;/sup&gt;) or</td>
</tr>
<tr>
<td>4. Multiple meningiomas (two or more) and two of unilateral VS, cataract, glioma, neurofibroma schwannoma, cerebral calcification or</td>
</tr>
<tr>
<td>5. Constitutional or mosaic pathogenic NF2 gene mutation in blood or identical mutations in two distinct tumors&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: FDR = first-degree relative; UVS = unilateral vestibular schwannoma; VS = vestibular schwannoma

Ideally LZTR1 testing should be carried out on tumor tissue, but as mosaicism does not appear as common in LZTR1-affected individuals, blood will still give a useful result and probably exclude a germline schwannomatosis condition.

<sup>a</sup>2016 suggested revisions.

<sup>b</sup>Any two includes two of any tumor type such as schwannoma.
Once tumors are detected, cranial MRI should be performed annually. Otherwise, screening every 3 to 5 years is sufficient. Both surgical resection and stereotactic radiation are used as treatment for symptomatic tumors. There is growing evidence that bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, can reduce schwannoma size and improve hearing in patients with an acoustic schwannoma.

**Tuberous Sclerosis**

Tuberous sclerosis complex (TSC) is caused by a mutation in the TSC1 (chromosome 9q34) or TCS2 (16p13.3) genes. TSC1 and TSC2 encode hamartin and tuberin proteins, respectively. Approximately 80% of cases are de novo, while the other 20% are autosomal dominant. The hamartin-tuberin complex is important in regulating mechanistic target of rapamycin (mTOR) pathways, and disruption of this pathway can lead to TSC-associated tumors. The gene expression and clinical phenotypes are highly variable.

Like NF, diagnosis can be made clinically or by genetic testing. Definite TSC diagnosis requires two major clinical features, or one major and two or more minor clinical features. Possible TSC implies that a patient has either one major clinical feature or two or more minor clinical features (Table 6).

**Table 6. Major and Minor Diagnostic Criteria for Tuberous Sclerosis**

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypomelanotic macules (≥3, at least 5 mm diameter)</td>
<td>• “Confetti” skin lesions (1 mm–2 mm hypomelanotic macules)</td>
</tr>
<tr>
<td>• Angiofibromas (≥3) or fibrous cephalic plaque</td>
<td>• Dental enamel pits (≥3)</td>
</tr>
<tr>
<td>• Ungual fibromas (≥2)</td>
<td>• Intraoral fibromas (≥2)</td>
</tr>
<tr>
<td>• Shagreen patch (connective tissue nevus)</td>
<td>• Retinal achromatic patch</td>
</tr>
<tr>
<td></td>
<td>• Multiple renal cysts</td>
</tr>
</tbody>
</table>
- Multiple retinal hamartomas
- Cortical dysplasias (includes tubers and cerebral white matter radial migration lines)
- Subependymal nodules
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma
- Lymphangioleiomyomatosis (LAM)
- Angiomyolipomas (≥2)

<table>
<thead>
<tr>
<th>Nonrenal hamartomas</th>
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</table>

Seizures affect up to 90% of patients with TSC, and epilepsy management can be difficult in these patients. Infantile spasms are often the first presenting seizure type. Adrenocorticotropic hormone (ACTH) is considered standard treatment for infantile spasms, although recent studies support vigabatrin as being even more effective in cases associated with TSC. Frequent MRI screening should be obtained during childhood and early adulthood to evaluate for subependymal giant cell tumors. Depending on location and symptoms, surgical resection or treatment with the mTOR inhibitor everolimus may be indicated.

**Sturge-Weber Syndrome**

Sturge-Weber syndrome is a congenital vascular disorder caused by somatic mutations in the *GNAQ* gene. The diagnosis is made when leptomeningeal angiomas are identified and are associated with a facial port-wine stain. Clinical symptoms include seizures, hemiparesis, visual field deficits, intellectual disability, and glaucoma.

The clear majority of port-wine stains are not associated with Sturge-Weber syndrome; in fact, port-wine stains can occur in up to 0.3% of newborns. Those associated with Sturge-Weber syndrome are typically seen in the V1 and V2 distribution.
but may occur throughout the body. Leptomeningeal angiomases are mostly seen in the posterior cerebrum, ipsilateral to the facial lesion.

Since most facial port-wine stains are not associated with leptomeningeal angiomases, and many intracranial angiomases are not detected on MRI in early infancy, imaging is not recommended at the time of birth. Infants with characteristic facial lesions should be monitored clinically throughout the first year of life, and imaging should be performed at 1 year or sooner if seizures occur or developmental delay is noted.

Prognosis depends on the extent of cerebral involvement. Some patients with intractable seizures may require hemispherectomy. Low-dose aspirin may be helpful in preventing cerebral ischemia; although data are quite limited, there does not appear to be an increased risk of intracranial hemorrhage in affected individuals.
Annotated Bibliography


Berry-Kravis E. Epilepsy in fragile X syndrome. Dev Med Child Neurol 2002;44(11):724–728. doi:10.1111/j.1469-8749.2002.tb00277.x. This article discusses a study determining the seizure frequency and type in 136 individuals with fragile X syndrome. The findings were consistent with the reported estimate of epilepsy occurring in 10% to 20% of individuals with fragile X syndrome.


This article gives a review of Rett syndrome, focusing on the prevalence and management of comorbid seizures.


This article provides an excellent summary of neurofibromatosis type 2, including epidemiology, genetics, diagnosis, and management.


This article discusses guidelines for the diagnosis and management of neurofibromatosis type 1. The consensus was based on published clinical studies and the pooled knowledge of experts in the field.


This thorough review of 43 studies addresses the prevalence of pervasive developmental disorders. The authors report a prevalence of 60 per 10,000 to 70 per 10,000 and note that the prevalence has increased in recent decades. Note that the article was written prior to
the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, revised criteria of autism spectrum disorders.

This paper discusses evidence-based standardized approaches for management of patients with tuberous sclerosis complex.

This article provides a comprehensive review of speech and language development and an overview of basic developmental milestones in children with Down syndrome.

This article provides a chart review of 58 subjects with Sturge-Weber syndrome on aspirin. The authors support low-dose aspirin use to optimize neurodevelopmental outcome.

This excellent article characterizes the spectrum of malformations of cortical development in 109 children with previously identified malformations of cortical development.


This important paper from 1968 led to the standard use of the Nellhaus head circumference growth chart for determining head circumference percentiles in children.


This article provides an excellent up-to-date review of the diagnosis and treatment of toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex (TORCH) in the newborn.


This article presents a retrospective analysis of 31 patients with neurofibromatosis type 2 who received bevacizumab for progressive vestibular schwannomas. The authors
concluded bevacizumab treatment improved hearing and reduced the size of the tumor in over 50% of patients.

This article gives an overview of Chiari malformations, specifically addressing the pathogenesis and genetic factors that contribute to the abnormal development.

This recent study reviewed genetic data from the Manchester NF2 database, and revised diagnostic criteria to exclude LZTR1-related schwannomatosis. This new diagnostic criteria replaces the original and revised Manchester criteria, taking into consideration that some unilateral vestibular schwannomas are due to LZTR1 mutations.

This article presents results of a study that evaluated 65 infants with hypotonia and found a prevalence of Prader-Willi syndrome in 10.7% (seven subjects). The recommendation is always to consider genetic testing for Prader-Willis syndrome in infants with hypotonia of unknown etiology.
This article provides an excellent summary of the clinical and genetic features of Angelman syndrome. It includes tables that are helpful for review. Some of the genetics, however, may be outdated as this article was published in 2005.