1 Central Nervous System Manifestations of Chromosomal Change

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Introduction

A wide variety of morphologic and functional abnormalities have been identified in the central nervous systems (CNS) of patients with chromosomal defects. These are reviewed for the more commonly encountered karyotypes, with emphasis given to those aberrations in chromosome number (e.g., trisomy, monosomy) or chromosome morphology (i.e., large deletions and duplications) that affect the CNS. Disorders associated with mosaicism, lesser chromosomal changes (including translocations), or single gene mutations are not included.

Chromosomal changes are encountered in early pregnancy loss, but their true incidence is hard to determine. A commonly used estimate is 50%. Alterations like trisomy 16 (estimated to occur in 1% of all conceptuses) are unlikely to come to the attention of neuropathologists because of early fetal demise. The prevalence of chromosomal defects is summarized for common CNS anomalies in Table 1.1. Because of genetic mechanisms (e.g., incomplete penetrance and variable expressivity) and other factors, phenotypes do not always correlate precisely with specific karyotypes. For this reason, the tables in this chapter are limited to general summaries.

The craniofacial complex

While this chapter is oriented toward the description of changes in the CNS, the cranium can scarcely be ignored. The embryogenesis of brain and cranium proceeds in tandem and anomalies of one structure are almost always reflected by changes in the other.

The pathologist whose study of the CNS is hampered by severe autolysis, commonplace in stillbirth, or delivery by dilatation and evacuation, does well to examine the cranium to get clues to CNS pathology [1]. Two examples are anencephaly and holoprosencephaly. In the former, the cranial base is markedly flattened, much of the calvaria is absent, and sphenoidal anomalies are common. In specimens altered by holoprosencephaly, the anterior cranial fossa is flattened, cribriform plates are small, obscured, or absent, the crista galli is reduced in size or absent, and the anterior falx cerebri is absent or hypoplastic (Figure 1.1). Axial anomalies are especially common in trisomy 13 and 18. Identifying any of these changes is of great help in achieving a diagnosis, or at least in attempting to corroborate prenatal imaging studies.

Genetic counseling and the neuropathologist

Affected individuals and/or their families desire to understand both present and future issues surrounding their condition. Families are concerned about implications for present and future care, as well as prevention, recurrence risk, and family planning. Neuropathologists should be integral members of the team that provides information to patients and their families. Specialists will serve their patients well by providing information that is of direct use to the genetic counselor. In addition to written reports, the pathologist should provide photographs, especially of external phenotypic features (face, head, hands, and so forth), that have diagnostic value. Ethical ramifications are considerable, but beyond the scope of this review.

Autosomal trisomy

A trisomic cell is defined by the presence of three homologous chromosomes. The condition is serious and often associated

Developmental Neuropathology, Second Edition. Edited by Homa Adle-Biassette, Brian N. Harding, and Jeffrey A. Golden.

Table 1.1 Prevalence of chromosomal abnormalities in common central nervous system (CNS) anomalies.

CNS anomaly	Estimated Prevalence of Abnormal Karyotype (%)	Predominant Karyotypic Abnormality	Reference
Anencephaly	9	Variable, including trisomy 13, 18, and triploidy	26
Holoprosencephaly	50	Trisomy 13, 18	27
Dandy-Walker malformation	45–55	Trisomy 9, 13, 18, 21; triploidy; del(6p)	28
Complete vermian agenesis	32		28
Inferior vermian agenesis	53		28
Chiari malformation	Occasional	Trisomy 13, 18	26
Microcephaly/micrencephaly	Frequent	Trisomy 9, 13, 18, 21; sex chromosome trisomy or monosomy	26
Isolated ventriculomegaly	12	Trisomy 21; 47XXY	29
Agenesis of corpus callosum	18	Trisomy 8, 13, 18; del(11q)	26,30
Spina bifida/myelomeningocele	17	Trisomy 13, 18; triploidy	31
Coloboma	Often unspecified; 10% in 1993 study	Trisomy 13, 18; triploidy; 5p-; 4p-	32
Micro-/anophthalmia	25+	Trisomy 13	33

with prenatal demise, or live birth with multiple anomalies, some of which are life-threatening. Females with trisomy 13 or 18 have severe ovarian dysgenesis, resulting germ cell failure, and cannot reproduce, should they survive to reproductive age [2]. Women with trisomy 21 who become pregnant give birth to infants with trisomy 21 in about one-third of cases; affected males are sterile. Trisomic conditions with associated changes of the craniofacial complex and CNS are described below and summarized in Table 1.2.

Trisomy 8

Complete trisomy 8 is observed in first-trimester terminations of pregnancy and rarely thereafter. By contrast, survival to term or beyond with mosaic trisomy 8 is more common. The severity of phenotypic change does not appear to depend upon the percentage of trisomic cells, and thus, the phenotypes of complete and mosaic trisomy 8 are similar. The frequency is estimated to be between 1:25 000 and 1:50 000 live individuals; males are five times more commonly affected. Patients may manifest psychomotor restriction, seizures, or personality disorders; they have dysmorphic facies, with prominent forehead, widely spaced and deeply set eyes, broad nasal root, micrognathia, thick lips, and large protuberant ears [3]. Agenesis or hypoplasia of the corpus callosum is the chief alteration of the CNS; spina bifida occulta is observed, as well as a number of less common malformations.

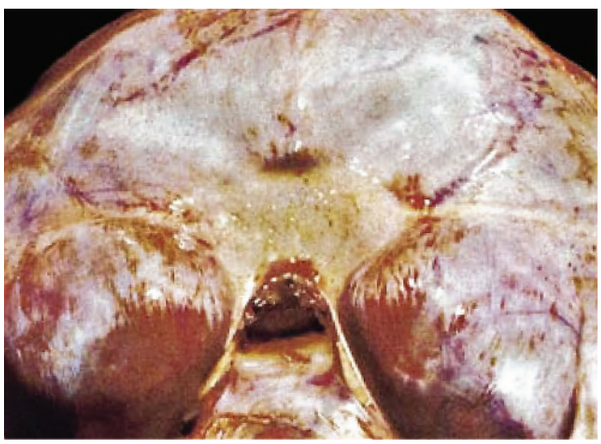

Figure 1.1 Close view of cranial base, showing anterior and middle cranial fossae of patient with holoprosencephaly and trisomy 13. Note absence of ethmoid derivatives (crista galli, cribriform plates) and falx cerebri. In cases of ocular hypotelorism, the basisphenoid and sella turcica may be narrowed.

Trisomy 9

Most newborns with trisomy 9 die in the perinatal period. Survivors have mental and motor deficiencies, and fail to thrive. Variable degrees of mosaicism are thought to modulate the severity of changes noted in the condition. The CNS is abnormal most of the time, and most consistently shows a Dandy-Walker malformation, although it has been well characterized morphologically in only a few cases [4]. Craniofacial changes may be nonspecific or those associated with holoprosencephaly.

Trisomy 13

Trisomy 13 is the third most common autosomal trisomy, with a prevalence variably reported as 1:5000 to 1:29 000 live births [5]. Like other aneuploid conditions, the spontaneous death rate is increased dramatically, both prenatally and perinatally; mean postnatal survival is 2.5–4 days. Diploid–aneuploid mosaicism confined to the placenta may affect intrauterine survival, and, inexplicably, mothers often suffer preeclampsia, which may contribute to spontaneous pregnancy loss [6].

Table 1.2 Craniocerebral findings in selected autosomal aneuploid conditions.

Karyotype	Craniofacial Findings	Morphologic and Functional Abnormalities of CNS
Trisomy 8	Scaphocephaly; prominent forehead; ocular hypertelorism; deeply set eyes; bulbous nose; thickened, everted lower lip; high or cleft palate; low set, dysplastic ears; micrognathia	Variable psychomotor restriction; personality disorder/psychosis; agenesis of the corpus callosum; spina bifida occulta; less frequent CNS changes: aqueductal stenosis; abnormal falx cerebri; Dandy–Walker malformation or isolated hypoplastic cerebellum; eye changes (variable): microphthalmia; strabismus; coloboma; corneal/lens opacity; glaucoma
Trisomy 9	Microcephaly, dolichocephaly; widening of cranial sutures; deep-set eyes; small palpebral fissures; bulbous nose, with broad base; low set, anomalous ears; micrognathia	Growth restriction; Dandy–Walker malformation; holoprosencephaly; lissencephaly; ventriculomegaly/ hydrocephalus; agenesis of corpus callosum; hypoplasia of septum pellucidum; cortical migration anomalies (including subpial glial nodules, pachygyria); simplified inferior olivary nuclei, abnormal hippocampal formation; germinal matrix cysts; syringomyelia; myelomeningocele; eye changes: anophthalmia; retinal or iridal coloboma; hypoplasia of optic nerves
Trisomy 13 (Patau syndrome)	Microcephaly; trigonocephaly; holoprosencephalic facies (e.g., cleft lip/palate; cebocephaly; ethmocephaly; cyclopia); cutaneous scalp defects; dysplastic ears	Holoprosencephaly (most common); Chiari malformation; hypoplastic cerebellum; neuronal migration defects; spina bifida; eye changes: microphthalmia; coloboma; retinal dysplasia; aniridia; hypoplastic optic nerve
Trisomy 18 (Edwards syndrome)	Microcephaly; 'strawberry-shaped' skull; broad, high forehead; low set, dysplastic ears and temporal bone anomalies; small nose and mouth; choanal atresia; cleft lip/palate; micrognathia	Partial or complete absence of the corpus callosum; Chiari malformation; neural tube defects (myelomeningocele, anencephaly); holoprosencephaly; neuronal migration defects; choroid plexus cysts; eye changes (less common): coloboma; cataract; cloudy cornea; retinal hypopigmentation; microphthalmia; iridal hypoplasia
Trisomy 21 (Down syndrome)	Incomplete ossification of calvaria; hypertelorism; cleft lip and/or palate; micrognathia; low set, malformed ears	Hydrocephalus, holoprosencephaly, hypoplasia of basal ganglia, cerebellum, occipital lobes, or other focal structure; lumbar myelomeningocele; less often: Chiari or Dandy–Walker malformation, hydranencephaly. Eyes: ocular coloboma, microphthalmia, anophthalmia, corneal clouding, cataract
Triploidy (69,XXX or 69,XXY)	Incomplete ossification of calvaria, with enlarged fontanelles; facial dysmorphism associated with holoprosencephaly; 'Harlequin' orbits; low nasal bridge; choanal atresia; preauricular malformations; cleft lip/palate	Intrauterine growth restriction; all varieties of holoprosencephaly; hydrocephalus; hydranencephaly; hypoplasia of basal ganglia, occipital lobes, or cerebellum; choroid plexus cysts; cavum septi pellucidi; less common: Chiari or Dandy–Walker malformation; eye changes: micro- or anophthalmia; proptosis; hypoplasia of iris or retina; coloboma; corneal clouding; cataract
Tetraploidy (92,XXXX or 92,XXYY)	Microcephaly; prominent, narrow forehead; low set ears; preauricular ear tags; beaked nose; micrognathia; cleft lip/palate	Severe pre- and postnatal growth restriction; severe mental restriction; hydrocephalus; Chiari malformation; myelomeningocele; arhinencephaly; eye changes: micro- or anophthalmia; cloudy cornea; coloboma

CNS, central nervous system

Phenotypic changes are well recognized (Table 1.2) and involve the CNS (Figures 1.2, 1.3, 1.4), craniofacial complex, axial skeleton, and multiple extracranial tissues. The most common CNS manifestations among this group are holoprosencephaly and anencephaly.

Trisomy 18

The incidence of trisomy 18 is given as 0.3 per 1000 live births, with a female to male ratio of 3:1. Cranial and brain abnormalities are common, as are eye malformations, axial, hypophyseal, and extracranial anomalies [3].

Trisomy 21

The literature on Down syndrome and descriptions of CNS changes are voluminous, although probably not entirely reliable, in that older cases were not confirmed by karyotyping. Because phenotypic variability is substantial, diagnosis is not always possible by physical examination, especially in the

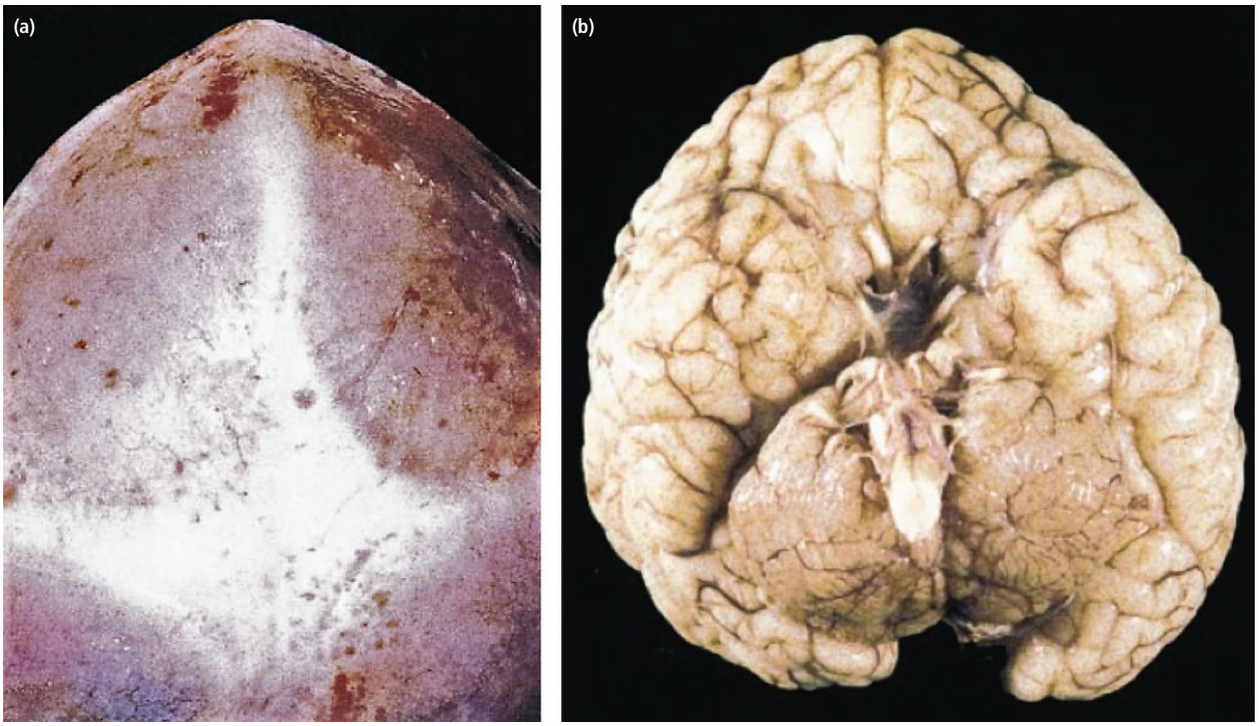

Figure 1.2 Two term infants with trisomy 13. (a) Superior view of calvaria (after reflection of scalp) altered by trigonocephaly and partial metopic craniosynostosis. (b) Basal view of deformed brain from patient with trigonocephaly; note absence of olfactory tracts (arhinencephaly), asymmetric optic nerves, and dysplastic cerebellar folia.

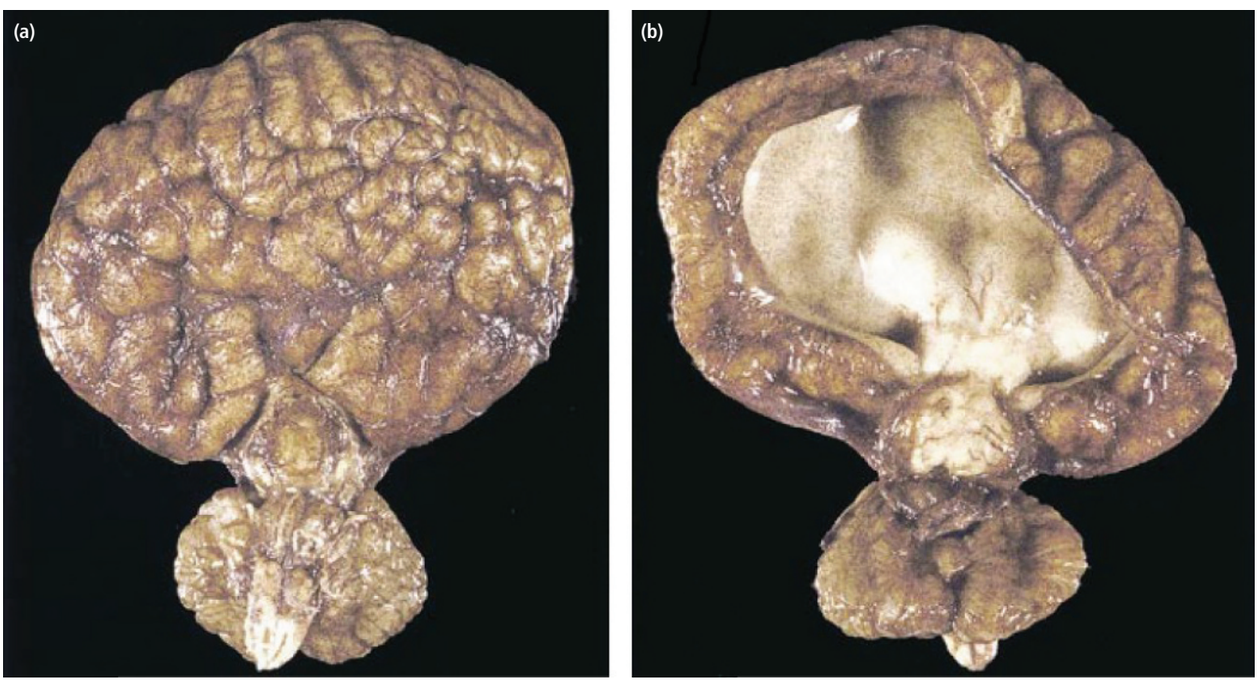

Figure 1.3 Infant with trisomy 13. (a) Basal view of brain with holoprosencephaly. (b) superior view of same brain. Note fusion of frontal lobes and lateral ventricles.

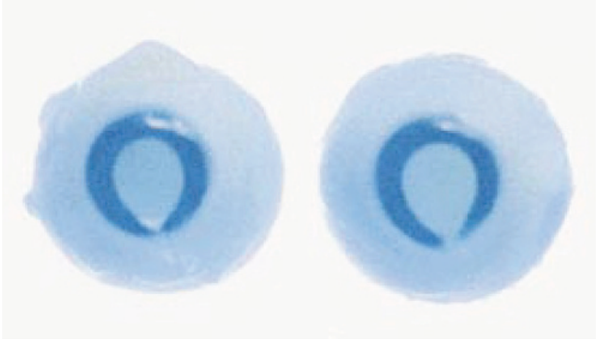

Figure 1.4 Coloboma is encountered frequently in patients with chromosomal abnormalities. Iridal colobomata are shown from a newborn infant with classic findings of trisomy 13.

prenatal period. The condition is rather common, with estimates generally given at about 1.3 per 1000 live births. About 95% of patients have 47,+21 karyotypes, while the remainder are mosaic or manifest unbalanced translocations (mostly Robertsonian).

The cranium is round (brachycephaly) and the brain likewise, with foreshortened frontal poles and a flattened occiput; the superior temporal gyrus is often small and straight (Figure 1.5). Brain weight is usually reduced by 20–25% after the first 2 years. A variety of dendritic abnormalities have been identified. The most consistent findings are reduced complexity and numbers of dendritic branches and spines after 1–2 years of age. Patients suffer early dementia leading to Alzheimer-type changes in the brain.

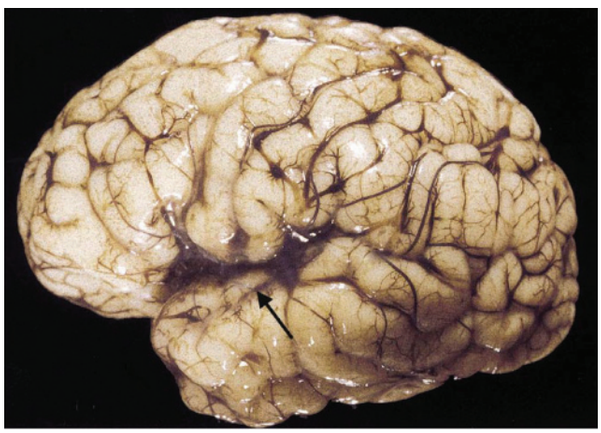

Figure 1.5 Lateral view of brain of newborn infant with trisomy 21. Note mild blunting of frontal lobe and abnormally small superior temporal gyrus, common findings in this condition. The middle temporal gyrus is enlarged.

Other autosomal aneuploidies

Triploidy

The most common chromosomal abnormality observed in first-trimester spontaneous miscarriages is a complete, supernumerary set of chromosomes, or triploidy, occurring in 12% of all such fetuses. Affected individuals (69,XXX or 69,XXY), who may be mosaic or manifest complete trisomy, survive occasionally to term, then die in the immediate postnatal period. Increased nuchal translucency and characteristic placental abnormalities (enlarged placenta with hydatidiform degeneration, or a small placenta in cases of digyny (i.e., a diploid ovum fertilized by a monoploid sperm), are noted by prenatal ultrasound. Intrauterine growth restriction is also common, as are a wide variety of well-known craniofacial, CNS (Figures 1.6 and 1.7), and extracranial anomalies. Syndactyly of the third and fourth fingers, or first and second or third and fourth toes, occurs in 50% and 30% of individuals, respectively, and should compel

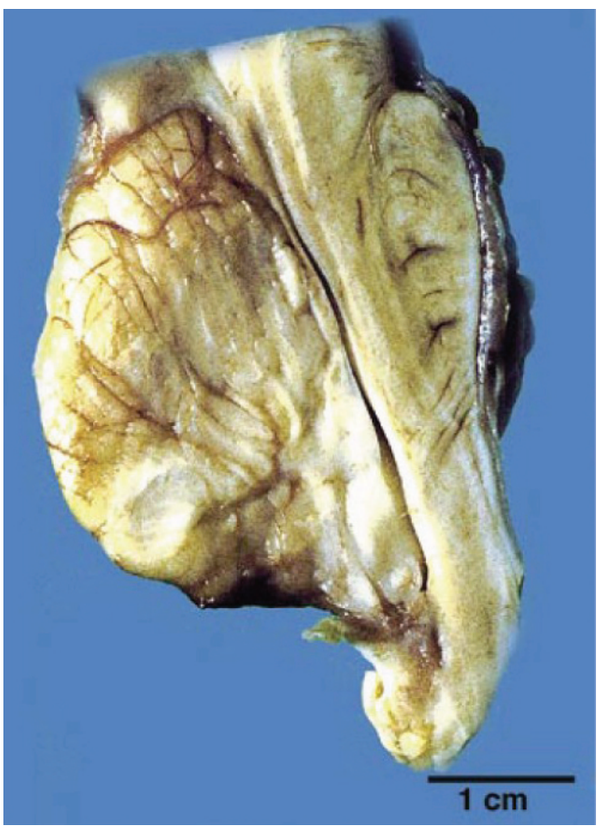

Figure 1.6 Median section of cerebellum and brainstem altered by Chiari malformation. Note small size of cerebellum and caudal herniation of the cerebellum and medulla, unrolled posterior medullary vellum, beaking of colliculi, and herniation of brainstem; the fourth ventricle is nearly obliterated.

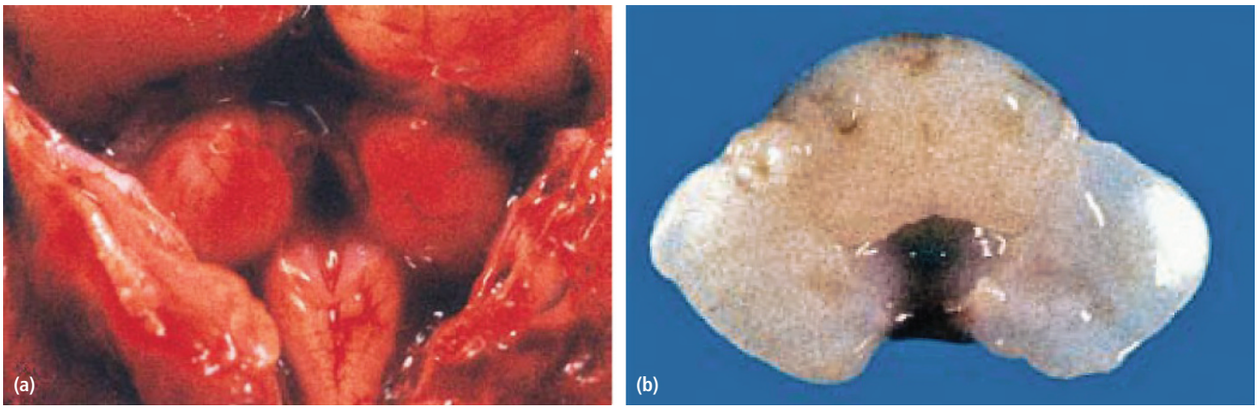

Figure 1.7 Dandy–Walker malformation. (a) In situ demonstration of absent cerebellar vermis. (b) Horizontal section of cerebellum, with midline space representing absence of vermis.

the pathologist to obtain a karyotype. Tissue other than blood should be cultured, as triploid cells are eliminated selectively from lymphocytes. Flow cytometry is an efficient way of reaching a diagnosis, in that the quantity of DNA measured by the process will be increased by 50%.

Tetraploidy

Like triploidy, tetraploidy (92,XXXX or 92,XXYY) is also associated with early loss. Together, the two conditions account for 30% of karyotypically abnormal spontaneous miscarriages. Growth and mental restriction and a wide variety of craniofacial and CNS anomalies are found in affected patients.

Sex chromosome aneuploidy

Patients with alterations in the number of X or Y chromosomes oftentimes manifest normal development. However, an increased risk for gonadal dysgenesis and decreased fertility are also recognized, as is developmental delay involving speech, motor abilities, and learning. Phenotype, including behavior, is affected in patients with sex chromosome aneuploidies, but the severity does not correlate with the magnitude of aneuploidy. Mental restriction, schizophrenia, and bipolar disorders have all been associated variably with sex chromosome aneuploidy. It is impossible to assign prognosis with certainty. Although specific neuropathological changes are not well defined, sporadic anomalies are reported and summarized in Table 1.3.

Deletions

Deletions arise from a variety of mechanisms. They involve absence of the terminal or interstitial regions of the chromosome, leaving a haploid DNA content for the affected segment, and for this reason were referred to as "monosomy" in older citations. Deletions may appear de novo as isolated anomalies, may result from de novo inversions, or may be inherited as familial translocations or inversions. The magnitude of phenotypic or functional deficit may or may not correlate with the size of deletion. The recurrence risk for deletion syndromes in siblings is generally negligible, unless a parent is a translocation carrier. Offspring of balanced translocation carriers may inherit balanced translocations or deletion (or duplication) syndromes. Carriers of balanced translocations do not, as a rule, have severely altered phenotypes. Affected patients, if able to reproduce, may transmit deletions.

The absence of genetic material has, in some instances, compelled researchers to hypothesize haploinsufficiency as a pathogenetic mechanism. Clearly, knowledge of breakpoints and exact genes that are lost is important to understanding genotype/phenotype correlations. The contribution of subtelomeric deletions to CNS development and function is important. Patients with terminal deletions may exhibit phenotypes that differ from those with interstitial phenotypes. General statements regarding the more common deletion syndromes, with anatomic and functional details, are provided in Table 1.4.

Deletion 3p-

Patients with 3p- deletions are rare and have an equal sex ratio. Growth restriction and developmental delay are major findings, and, like patients with many deletions, survival depends upon the severity of anomalies. The gene *MEGAP* is lost in 3p- and this gene is thought to play an important role in cognition, learning, and memory, presumably by regulating the cytoskeleton, axonal branching, and neuronal migration [7].

Deletion 4p-

Patients with deletions of the short arm of chromosome 4 (Wolf-Hirschhorn syndrome) occur infrequently (1:50 000 live births), with a female: male ratio of 2:1. Infants may manifest intrauterine growth restriction and hypotonia at birth; 35% die in the

Table 1.3 Craniocerebral findings in selected sex chromosome aneuploidies.

Karyotype	Craniofacial Findings	Morphologic and Functional Abnormalities of CNS
45, X0 (Turner syndrome or Ullrich-Turner syndrome)	Facies without expression; low posterior hairline; ocular hypertelorism; downslanting palpebral fissures	Pre- and postnatal growth restriction; eye changes (frequent): strabismus; ptosis; learning difficulties, including visual-spatial and perceptive deficits; psychiatric impediments, but no psychopathology
47,XXX (triple-X or trisomy X)	Often phenotypically normal (tall stature common); uncommon dysmorphic features: ocular hypertelorism; epicanthal folds; depressed nasal bridge	Poor motor skills; learning disabilities and language delay in some patients; mental restriction possible, but highly variable
47,XYY	Often phenotypically normal (tall stature common); increased craniofacial dimensions by cephalometry	Learning disabilities, including speech delay and autism; behavioral delay is inconsistent; hyperactivity; increased risk for schizophrenia or bipolar disorder; intention tremor; hypotonia; hypoplastic or absent corpus callosum; ventriculomegaly; Dandy–Walker malformation
47,XXY (Klinefelter syndrome)	Feminization; tall stature	Normal intelligence quotient, but reading deficiency and poor spelling in two-thirds of patients; reduced control of impulses and poor motor coordination; dyslexia, attention-deficit disorder, or psychiatric disorders, including psychosis, in some
48,XXXX (tetra-X s. or tetrasomy X)	Tall stature; dull, flat facial expression; ocular hypertelorism; flat nasal bridge; epicanthal folds	Intrauterine growth restriction; mild to moderate mental restriction; emotional disturbances; eye changes: strabismus, iridal coloboma; myopia
49,XXXXX (penta-X s. or pentasomy X)	Microcephaly; coarse facies, with epicanthal folds; upslanting palpebral fissures; broad, depressed nasal bridge; ocular hypertelorism; low set, malformed ears; low posterior hairline; cleft palate; micrognathia	Growth restriction (uncommon); severe psychomotor restriction
49,XXXXY	Microcephaly; plagiocephaly; trigonocephaly; many traits shared with pentasomy X, including: epicanthal folds; upslanting palpebral fissures; ocular hypertelorism; midface hypoplasia; low nasal bridge; cleft soft palate; micrognathia	Intrauterine and postnatal growth restriction; delayed ossification; mental restriction; psychomotor delay; psychiatric/personality disorders, including cognitive impairment; aggressiveness, self-inflicted injury; severely delayed or absent speech

CNS, central nervous system

first 2 years of life. Survivors have seizures that can be constant and severe psychomotor restriction; they have been described as being without personality. It is possible, however, that the condition is more common than previous estimates. It has probably been misdiagnosed at times (for example, midline scalp defects, facial clefts, and coloboma in a subset of patients may be confused with trisomy 13) and only about one-half are recognized by routine banding techniques [8]. Thus, prognosis may not be as poor as believed previously. Only a few adults have been described, but accurate diagnosis facilitates appropriate interventional care and counseling.

Deletion 5p-

Commonly known as *cri-du-chat* ("cat cry") syndrome, deletion 5p- is one of the most common deletion syndromes, occurring in 1:15 000 to 1:50 000 live births and constituting nearly 1% of all institutionalized patients; a slight female preponderance is recognized, with a male to female ratio of 0.72 [3]. Findings evolve as patients age. Infants exhibit a high-pitched or mewing, cat-like cry, which disappears in childhood as the orientation of posteriorly approximated vocal cords changes. Similarly, the rounded face becomes thinner and more asymmetric. Speech and language development are delayed, sometimes severely.

Deletion 9p-

Deletion 9p- is well defined clinically, with over 100 cases published; a female predilection of 2:3 to 3:4 has been reported [3]. Nonspecific facial dysmorphia, hypotonia (or occasional hypertonia), psychomotor and mental restriction are common, and a particular neurobehavioral profile is recognized. The eyes can slant either upward or downward; infants with the former can be confused with patients with trisomy 21. As with del (5p), facial abnormalities become less obvious with age.

Deletion 11q-

Patients with deletions of the long arm of chromosome 11 (Jacobsen syndrome) manifest psychomotor restriction and a variety of nonspecific changes of the craniofacial complex. Some 32 cases have been reported; the condition has a strong female preponderance. Over one-half of patients manifest a variety of

Table 1.4 Craniocerebral findings in selected deletion syndromes.

Deletion	Craniofacial Findings	Morphologic and Functional Abnormalities of CNS
3p-	Microcephaly; dolichocephaly; synophrys; angulated face; ocular hypertelorism; short, broad nose; low set, dysplastic ears; micrognathia	Pre- and postnatal growth restriction, with severe developmental, psychomotor, and speech delay; ptosis
4p-	Also known as Wolf–Hirschhorn syndrome; microcephaly; dolichocephaly; midline scalp defect; cleft lip and/or palate; 'Greek helmet' facies, with ocular hypertelorism; frontal bossing; hypoplastic orbits; epicanthal folds; beaked nose with broad ridge; midline scalp defect; preauricular dimples; small mouth; dental anomalies	Postnatal growth restriction; severe psychomotor restriction; seizures; eye changes: ptosis, strabismus, nystagmus, coloboma
4q-	Microcephaly; abnormal cranial contour; ocular hypertelorism; epicanthal folds; depressed nasal bridge, with anteverted nares; Robin sequence, with cleft lip/palate and retro- or micrognathia; low set, posteriorly rotated, pointed ears	Postnatal growth restriction; mild to moderate mental restriction; hypotonia; seizures; sensorineural hearing loss and oculomotor nerve palsy (latter findings in one patient)
5p-	Also known as *cri du chat* syndrome; microcephaly; round face, with ocular hypertelorism and low set, posteriorly rotated ears that evolves after infancy to a thin, asymmetric face; epicanthal folds (more common in young); wide, depressed nasal bridge; micrognathia	Severe growth and mental restriction; hypotonia in infancy changes over time to hyperactive reflexes; ventriculomegaly; strabismus; tortuous retinal vessels/optic atrophy in adults
9p-	Trigonocephaly; flattened occiput; depressed temples; ocular hypertelorism, with variably slanted eyes; exophthalmos; microphthalmia; epicanthal folds; low set ears with dysplastic or aplastic lobes; choanal atresia; short nose with flattened bridge; midface hypoplasia, with small mouth; cleft palate; long philtrum	Developmental delay, with variable degree of psychomotor and mental restriction; both hypotonia and hypertonia reported; seizures; autism; hypoplastic corpus callosum; large cisterna magna
11q-	Also known as Jacobsen syndrome; trigonocephaly; telecanthus; ocular hypertelorism; broad, depressed nasal bridge; low set, dysplastic ears; micrognathia; palatal anomalies	Psychomotor restriction, with severe speech impairment; micrencephaly, with white matter deficiency (supratentorial); ventriculomegaly, with or without spina bifida (latter infrequent); cerebral atrophy; agenesis of corpus callosum; eye changes: iris coloboma; strabismus
13q-	Microcephaly; high, broad forehead; large, low set ears; depressed nasal bridge; protruding maxilla; micrognathia	Severe mental restriction and developmental delay; hypotonia; hydrocephalus; hydranencephaly; holoprosencephaly; agenesis of the corpus callosum; neural tube defects (lumbosacral myelomeningocele); eye changes: ptosis; microphthalmia; coloboma (iris or choroid); corneal opacity; cataract; retinoblastoma (in 18% of patients)
18p-	Facial changes may be non-specific (round face, ocular hypertelorism, large ears, broad nasal bridge, upturned nostrils, micrognathia) or those associated with holoprosencephaly (see text); also micro- or brachycephaly; craniosynostosis; choanal stenosis, cleft palate	Variable mental restriction; diabetes insipidus; holoprosencephaly; hypotonia; spinal muscular atrophy; aphasia/dysphasia; eye changes: ptosis, strabismus, nystagmus, microphthalmia, coloboma, cloudy cornea, cataract; hearing loss
18q-	Microcephaly; deeply set eyes; narrow/atretic ear canals; frontal bossing; midface hypoplasia; prominent chin; small 'carp' mouth	Hypotonia, with classic 'froglike' position of legs; mild to severe mental restriction; behavioral changes (see text) and seizures; ventriculomegaly secondary to volume loss and white matter disease (involving basal ganglia and/or thalami); holoprosencephaly; thinning of corpus callosum; hypotonia; hearing impairment; eye changes: strabismus, nystagmus, glaucoma, tapetoretinal degeneration, bilateral optic atrophy
21q-	Microcephaly; holoprosencephaly; downward slanting palpebral fissures; prominent nasal bridge; large, low set ears; cleft lip/palate; micrognathia	Variable growth and mental restriction; hypo- or hypertonia; sensorineural hearing loss; cortical atrophy; hypoplasia of cerebellum/brain stem; agenesis of corpus callosum; ventriculomegaly; eye changes: Peters anomaly of iris; microphthalmia; cataract

CNS, central nervous system

CNS abnormalities; some are structural, but others appear to represent deficient or delayed white matter formation [9]. A host of extracranial malformations are also recognized.

Deletion 13q-

Deletion 13q- is often lethal in early gestation. Surviving patients are rare, presenting in an estimated 2 in 100 000 births, with a gender ratio of 1:1 [10]. Growth restriction is common; mental restriction is moderate to severe [11]. Holoprosencephaly (*ZIC2*, mutated in some cases of holoprosencephaly, maps to 13q), hydranencephaly, and neural tube defects have been reported, and retinoblastoma is recognized commonly [12].

Deletion 18p-

Over 150 cases of deletion 18p- have been reported, with a male to female ratio of 2:3 [3]. Affected individuals show variable degrees of developmental delay and mental restriction, with consistent facial dysmorphism in infants and adults. Extracranial anomalies are variable as well, and include cardiac defects and endocrine dysfunction [13]. Patients with holoprosencephaly may exhibit any of the associated facial changes, including mild facial changes, cleft lip and palate, cebocephaly, and cyclopia. Of note, *TGIF*, one of the genes mutated in holoprosencephaly, maps to 18p. Focal or generalized dystonia and hypokinesia are observed, with distal spinal muscular atrophy reported.

Deletion 18q-

Deletion 18q- is one of the most common deletion syndromes (without sex predilection), and is manifest by tapered digits, facial dysmorphism, including deeply set eyes, dysplastic ears, and small, rounded, "carp" mouth. Hypotonia and growth failure are common. Decreased growth hormone production in patients suggests that a gene on 18q is involved in hormone production [14]. Correlated with this is the report of hypoplasia of the anterior pituitary gland [15]. Fifty to eighty percent of patients have sensorineural or conductive hearing loss, associated with malformations of the external and middle ears [16]. Intelligence is mildly to severely deficient, and behavioral problems include hyperactivity, aggressiveness, and temper tantrums; autism occurs in some patients, but probably not with increased incidence. By magnetic resonance imaging, white matter abnormalities involve periventricular and deep white regions (more pronounced in parieto-occipital areas), internal and external capsules, centrum semiovale, corona radiata, and subcortical regions. Changes are thought to result from incomplete myelination, most probably due to a missing copy (haploinsufficiency) of the myelin basic protein gene [17].

Deletion 21q-

Deletion 21q- has been called the "phenotypic countertype of trisomy 21," in that studies of affected patients who have reduced amounts of genetic material from chromosome 21 might shed light on those with increased amounts of material (i.e., those with Down syndrome). Phenotypic variation is considerable, and it is possible that a variety of conditions, including monosomy 21, have been reported inappropriately under this designation [3]. That being said, complete monosomy 21 is very rare, and phenotypic alterations probably arise from absence of the long arm [18]. Many findings are nonspecific [19].

Duplications

Pure duplications are rare. More likely, they result from unbalanced translocations, in which case, the duplication of material on one chromosome is accompanied by a deletion on another chromosome. This makes it difficult to attribute a given phenotype solely to the duplication. Selected syndromes are presented below, with specific findings provided in Table 1.5.

Duplication 3q+

Duplication 3q+ is a rare condition, known by about 40 published cases; it can resemble Cornelia de Lange syndrome. The male to female ratio is equal. A wide variety of craniofacial and CNS anomalies and functional alterations are recognized. The fingers can be held in a "trisomy 18 position" which can be confusing to the examiner [20]. The pure dup (3q) syndrome is rare, in part because most patients with the syndrome have unbalanced translocations, the deletion on another chromosome complicating analysis [21]. Affected patients have an extra copy of the *KCNMB3* gene, which shows sequence similarities to regulatory subunits of calcium-activated potassium channels; because of the importance of these channels in neuronal function, it is possible that overexpression is related to the seizures and restriction observed in patients [22]. Congenital heart defects are recognized.

Duplication 9p+

Duplication 9p+ is one of the most common partial trisomy syndromes, and is also known as Rethoré syndrome. Individuals have well-recognized features, of which ventriculomegaly and Dandy-Walker malformation (Figure 1.7) are prominent [23]. In fact, the prevalence of Dandy–Walker malformation in this condition has compelled some to suggest a dosage effect of genes located on chromosome 9 [24]. Abnormalities in neuronal migration are also recognized, including subcortical laminar (band) heterotopia or double cortex. The 100 or so cases known have occurred twice as often in females. A generalized delay in bone maturation is manifest by failure of timely closure of fontanelles and cranial sutures; however, catch-up growth often occurs [3]. Findings from magnetic resonance imaging in the single reported adult consist of underdeveloped white matter, atrophic corpus callosum, and choroidal fissure cyst [25].

Table 1.5 Craniocerebral findings in selected duplication syndromes.

Duplication	Craniofacial Findings	Morphologic and Functional Abnormalities of CNS
3q+	Microcephaly; brachycephaly or dolichocephaly; craniosynostosis or widely separated sutures, with large anterior fontanelle; hypertrichosis/synophrys/bushy eyebrows/long eyelashes; ocular hypertelorism; upslanted palpebral fissures; low set, malformed ears; broad nasal root; cleft palate; prominent philtrum; prognathism; micro- or retrognathia	Severe growth and mental restriction; seizures; micrencephaly; polymicrogyria; hypoplastic olfactory bulbs and tracts or arhinencephaly; cerebellar hypoplasia; hypoplastic corpus callosum; neuronal migrational defects; ventriculomegaly; aqueductal stenosis; hypoplastic pons; hypoplastic pyramidal tracts; gross spinal cord anomalies, including anomalous fissures, narrowing, or shortening; eye changes: strabismus; ptosis; microphthalmia; anophthalmia; cataract; coloboma; glaucoma
4p+	Microcephaly; prominent glabella/supraorbital ridge; ocular hypertelorism; bulbous nose, with depressed nasal bridge; ear abnormalities; prominent chin	Psychomotor restriction; postnatal growth restriction; seizures; respiratory and feeding problems; eye changes: anomalies reported (unspecified)
9p+	Also known as Rethoré syndrome; microcephaly; brachycephaly; delayed closure of fontanelles and cranial sutures; frontal bossing; ocular hypertelorism; deep-set, downslanting eyes; broad nose; large, low set, dysplastic ears; short, upper lip; cleft lip/palate; downturned corners of mouth	Mild to moderate developmental delay, especially language; variable mental restriction; hypotonia; Dandy–Walker malformation; ventriculomegaly/hydrocephalus (sometimes associated with seizures); aqueductal stenosis; polymicrogyria; subcortical band heterotopia (in one adult); underdeveloped white matter; hypoplastic corpus callosum; choroidal fissure cyst; eye changes: microphthalmia; Brushfield spots; keratoconus; strabismus; myopia; cataract; iridal coloboma; ectopic pupil/dislocated lens; optic nerve atrophy
10q+	Microcephaly; high forehead; small palpebral fissures; flat, broad nasal bridge; small upturned nose; midface hypoplasia; prominent philtrum; cleft palate; micrognathia; small mouth	Profound psychomotor and developmental delay; pre- and postnatal restriction; eye changes: blepharophimosis; scoliosis
15q+	Microcephaly; dolichocephaly; prominent occiput; downslanting palpebral fissures; large, low set ears; bulbous nose; long philtrum; small mouth, with micro- or retrognathia	Severe developmental delay, with postnatal growth restriction due in part to swallowing difficulties; distal 15q duplication may manifest hydrocephaly rather than microcephaly

CNS, central nervous system

Future perspective, conclusions

Clearly, a wide variety of morphologic and functional deficits affect the CNS of patients with chromosomal abnormalities. These changes are recognized in some detail, and continue to be delineated. However, while some embryologic and even genetic mechanisms are beginning to be identified, most conditions are poorly understood, and little is known about genotype/phenotype correlations. It will require the continue efforts of clinical workers and researchers alike to bring understanding and, it is hoped, prevention or cures to patients and their families.

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