Handbook of Clinical Neurology, Vol. 111 (3rd series)
Pediatric Neurology Part I
O. Dulac, M. Lassonde, and H.B. Sarnat, Editors

Chapter 13

Microcephaly

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INTRODUCTION

Microcephaly is defined as an occipitofrontal head circumference (OFC) ≤ -2 standard deviations (SD) below the mean for sex, age, and ethnicity. The term "true" or "severe" microcephaly is used for an OFC ≤ -3 SD. The term microencephaly refers to a brain weight 2 SD below the mean. The incidence of true primary microcephaly worldwide varies from 1.3 to 150 per 100 000 live births.

Several developmental processes that are under control of genetic and environmental factors play a role in sculpting the brain size. Any condition that affects important processes of brain growth such as progenitor cell proliferation, cell differentiation, and cell death can thus induce microcephaly (Barkovich et al., 2005). Microcephaly may be evident at birth (primary microcephaly) or postnatally (secondary microcephaly). Anomalies leading to microcephaly may exclusively affect the cerebral development (non-syndromic microcephaly) or are associated with visceral, and/or skeletal malformations, and/or facial dysmorphism (syndromal microcephaly). These terms do not imply distinct etiologies and both syndromal and non-syndromal forms may coexist with some etiologies (as in Fanconi anemia). Microcephaly can be acquired (i.e., caused by environmental factors) (Abuelo, 2007) or genetic.

ACQUIRED CONGENITAL MICROCEPHALIES

Acquired congenital microcephaly can occur after various injuries to the developing brain such as intrauterine infection, irradiation, exposure to drugs/toxins including maternal alcohol consumption (fetal alcohol syndrome), fetal irradiation, maternal hyperphenylalaninemia, placental insufficiency, and/or severe maternal illness (Table 13.1). Prenatal brain damage is believed to be a multifactorial, multihit process that varies in severity between individuals, affects infants of different genetic backgrounds, and occurs at various stages of the physiological developmental program. Tissue damage occurring early in pregnancy, especially in the first trimester of pregnancy, through infectious/toxic/ischemic processes may disturb subsequent brain development and result in macroscopic (malformation, disruption) and microscopic (dysplasia) developmental anomalies of the central nervous system (CNS) often associated with microcephaly. Acquired microcephaly is further discussed in depth in the next chapter.

PRIMARY MICROCEPHALIES

Primary microcephalies reflect an imbalance between progenitor cell production and cell death (Francis et al., 2006). Disruption of neural progenitor proliferation (defects in mitotic division or cell cycle regulation of progenitors) or of DNA damage response can lead to a reduced number of neuronal and glial cells within the brain.

Primary autosomal recessive microcephaly (MCPH): disorders of progenitor cell proliferation

Primary non-syndromal microcephaly that follows an autosomal recessive pattern of inheritance is also referred to

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Table 13.1

Common causes of acquired primary microcephaly

	Further brain malformations	Brain calcifications	Extraneurological malformations
Intrauterine infections			
Cytomegalovirus	Ventriculomegaly, subependymal cysts, migration disorders	+	Chorioretinitis, deafness, intrauterine growth retardation, oligoamnios, intestine hyperechogenicity
Herpes simplex*	Hydrocephaly, porencephalic cysts	+	Chorioretinitis, microphtalmia
Rubella	Subependymal cysts	+	Heart defects, deafness, cataract, retinopathy, intrauterine growth retardation
Toxoplasmosis*	Hydrocephalus (aqueduct stenosis)	+	Chorioretinitis, optic atrophy
Syphilis*	Hydrocephalus, pseudoparalysis	+	Deafness, pulmonary hemorrhage, teeth abnormalities
Varicella–Zoster	Hydrocephalus, cortical atrophy	−	Skeletal anomalies, intrauterine growth retardation, limb hypoplasia, microphthalmia, cataracts, chorioretinitis, cutaneous scarring
Acquired immunodeficiency syndrome*	Brain atrophy, ventriculomegaly, white matter abnormalities	+	
Drugs			
Alcohol†	Corpus callosum agenesis, abnormal gyration	−	Heart and kidney defects, deafness, scoliosis, growth delay, dysmorphic features
Cocaine	Intracranial hemorrhage, encephaloceles	−	Skull and heart malformations
Antiepileptic drugs (carbamazepine, phenytoin, barbiturates, sodium valproate)	Spina bifida	−	Heart malformation, dysmorphism of face and fingers, facial cleft, growth retardation
Maternal illness or pregnancy factors			
Phenylketonuria*	Abnormal migration	−	Heart malformation, growth retardation
Placental insufficiency Malnutrition Anemia Systemic illness	Porencephaly, periventricular leukomalacia	−	Cardiac defects

*Treatable fetopathies.
†Preventable fetopathies.

as primary autosomal recessive microcephaly or Micro-Cephaly Primary Hereditary (MCPH, historical synonym: *microcephalia vera*). MCPH is a rare and genetically heterogeneous disease reported in about 100 families worldwide. It has an incidence of 1:30 000 to 1:250 000 live births (Van den Bosch, 1959). To date, 11 MCPH loci have been mapped among which ten genes have been identified: *MCPH1* (MCPH1); *WDR62* (MCPH2); *CDK5RAP2* (MCPH3); *CASC5* (MCPH4); *ASPM* – the most commonly involved in humans – (MCPH5), *CENPJ* (MCPH6), *STIL* (MCPH7), *CEP135* (MCPH8), *CEP152* (MCPH9) and *CEP63*. The last MCPH locus is located in 10q11.23–21.3. These genes code for proteins associated with the centrosome. They play an important role in organization and orientation of the mitotic spindle in neural progenitors and in the assembly of microtubules at centrosomes and kinetochores during mitosis. For each of them, loss-of-function mutations have been identified (see Table 13.2 and for review Passemard et al., 2009a; Kaindl et al., 2010). Roughly 70% of primary recessive microcephalies are unlinked to known genes in Caucasian population.

MCPH can be detected *in utero* as soon as 24 weeks of gestation through ultrasound scan. Evaluation of the gyrification through fetal MRI is possible during the 3rd trimester. Historically, MCPH definition was very close to "microcephalia vera" from a phenotypic point of view. Diagnosis of MCPH is based on the following criteria: (i) OFC < -2 SD at birth and < -3 SD before 1 year of age; (ii) variable cognitive impairment, speech delay, hyperactivity, and attention deficit but no major motor delay and (iii) no neurological signs except mild seizures (10%) and sometimes pyramidal signs (Shen et al., 2005; Passemard et al., 2009a); (iv) absence of consistent associated anomalies, except facial dysmorphism secondary to narrow, sloping forehead (more common with severe microcephaly), and, sometimes, mild shortness of stature (height between -2 and -3 SD), mainly associated with *MCPH1* (Neitzel et al., 2002; Shen et al., 2005); and (v) reduction in brain volume, affecting both cortex and white matter, typically associated in many cases with a simplified gyral pattern (Desir et al., 2008; Passemard et al., 2009a), and in some cases with periventricular heterotopias, cortical dysplasia, polymicrogyria (Trimborn et al., 2004; Passemard et al., 2009a) or mild cerebellar hypoplasia (Passemard et al., 2009a). Cortical lamination is well preserved but neurons in layers II and III are depleted in fetuses with clinically diagnosed *microcephalia vera* (Evrard et al., 1989; Caviness et al., 2008). Language and behavioral therapy should be initiated early on, attention deficit and hyperkinesia can be treated with methylphenidate (Ritalin®), and seizures are usually responsive to antiepileptic monotherapy.

The nosology of MCPH has recently evolved with the discovery that loss of function mutations in some MCPH genes may cause primary microcephaly with dwarfism (Seckel syndrome). It has also been observed that mutation in MCPH gene resulted sometimes in cortical migration disorders or defect in cortical organization, meaning that this entity includes patients with a broader phenotypic presentation. Patients with *WDR62* mutations express awide spectrum of anomalies, from small, normally formed brain to pachygyria, lissencephaly, schizencephaly, polymicrogyria, and, in one instance, cerebellar hypoplasia (Bilguvar et al., 2011; Nicholas et al., 2011; Yu et al., 2011). *CEP152* and *CENPJ* are mutated in Seckel syndrome, a primordial dwarfism with microcephaly (Al-Dosari et al., 2010; Kalay et al., 2011). Clinical and imaging correlates for other MCPH genes remain scarce.

Microcephaly with DNA repair deficiency

Brain development can be severely affected by DNA repair defects (for review, see McKinnon and

Table 13.2

Primary autosomal recessive microcephaly

MCPH	Gene	Protein	Locus	OMIM
MCPH1	*MCPH1*	Microcephalin	8p23	251200
MCPH2	*WDR62*	WD repeat domaine 62	19q12	604317
MCPH3	*CDK5RAP2*	Cyclin dependent kinase 5 regulatory associated protein 2	9q33.3	608201
MCPH4	*CASC5*	Cancer susceptibility candidate 5	15q15.1	604321
MCPH5	*ASPM*	Abnormal spindle-like, microcephaly associated	1q31	605481
MCPH6	*CENPJ*	Centromeric protein J	13q12.2	609279
MCPH7	*STIL*	SCL/TAL1 interrupting locus	1p32	612703
MCPH8	*CEP135*	Centrosomal protein 135 kD	4q12	614673
MCPH9	*CEP152*	Centrosomal protein 152 kD	15q31.1	60432

Caldecott, 2007; McKinnon, 2009). Microcephaly is a common feature of defects in DNA double- and/or single-strand break repair (DSB, SSB) and in nucleotide excision-repair (NER) (see Table 13.3). In these disorders, mental retardation is a common, but not an universal feature. Defective repair of DSB can lead to Nijmegen breakage syndrome, Fanconi anemia, LIG4 syndrome, and human immunodeficiency with microcephaly (*NHEJ1* deficiency), all associated with an increased risk of malignancies. Defective response to SSB can result in ATR-Seckel syndrome (O'Driscoll et al., 2001) and microcephalic osteodysplastic primordial dwarfism type 2 (MOPD2) (Griffith et al., 2008; Rauch et al., 2008). Tumors are not increased in those syndromes, but early, life-threatening strokes are commonly recorded in children with MOPD2. Cockayne syndrome (Nouspikel, 2008), xeroderma pigmentosum (Kraemer, 2008), and trichothiodystrophy are the results of NER deficiency.

Microcephaly and dwarfism

Primary microcephaly is associated with severe intrauterine growth retardation and prenatal onset short stature (that can even progress after birth) in Seckel syndrome (O'Driscoll et al., 2003; Griffith et al., 2008), Meier-Gorlin syndrome, IGR and IGFR deficiencies, and microcephalic osteodysplastic primordial dwarfism type 2 (MOPD2 Rauch et al., 2008) (see Table 13.3). A severe form of microcephalic dwarfism (MOPD1 ot Taybi-Linder syndrome) with severe neurologic impairment and poor survival has been associated with a mutation in the *U4atac* small nucleosomal RNA, a component of the minor spliceosome ribonucleoprotein complex that includes proteins and small nuclear RNAs (snRNAs), catalyzes RNA splicing to produce mature messenger RNAs (Edery et al., 2011). A milder degree of short stature is observed with *MCPH1* and in *PQBP1*-related X-linked microcephaly-mental retardation syndrome.

Microcephaly with disturbance of neuronal migration

Neurogenesis occurs predominantly between the 8th and the 22–24th week of gestation, and neuronal migration between the 12th and the 25th week of gestation in humans. Both processes are thus overlapping during CNS development: several intrinsic factors that control neural progenitor's proliferation are critical regulators of cortical neuronal migration, explaining why microcephaly can be associated with abnormal migration. Secondary microcephaly may be associated with lissencephaly (thick, smooth cortex with disorganized cortical layering) or pachygyria (thick cortex with wide gyri, with abnormal cortical layering and shallow sulci). The major genes involved in the lissencephaly spectrum are *PAFAH1B1* (formerly *LIS1*), *DCX* (doublecortin), *RELN* (reelin), *TUBA1A*, and *ARX*. *TUBA1A* mutation should be suspected when lissencephaly/pachtgyria is combined with a fusion of caudate nucleus and putamen, missing anterior arm of the internal capsule, and cerebellar hypoplasia (Poirier et al., 2007). Mutations in *TUBB2B* (Jaglin et al., 2009), *ASPM* (Passemard et al., 2009b), *EOMES* (Baala et al., 2007), or *GPR56* (Sheen et al., 2004) have been reported in patients with microcephaly and polymicrogyria. Moreover, periventricular nodular heterotopias associated with microcephaly have been reported with *MCPH1* (Trimborn et al., 2004), *ARFGEF2* (Sheen et al., 2004), or *FLNA* (filamin A) mutations (Fox et al., 1998). The latter two are X-linked. *TUBB2B, TUBB3, TUBB5, GPR56* and *SRPX2* mutations are associated with various patterns of polymicrogyria.

Holoprosencephaly: microcephaly and disorders of telencephalic cleavage

Holoprosencephaly (HPE) is a birth defect in which the telencephalic vesicles emerging from the forebrain during the 5th and 6th week of development remains fused on the midline. HPE has an overall incidence of 1/250 in early fetal loss, but of 1/15 000 (Bullen et al., 2001) at birth. Abnormal cleavage of the vesicles leads to a wide spectrum of midline anomalies of the face, which are only partially correlated with the severity of the HPE. Facial anomalies extend from hypotelorism with a single upper central incisor, median cleft lip and palate (premaxillary agenesis), hypoplastic nose with single nostril (cebocephaly) to cyclopia (with synophthalmia and proboscis). It is subdivided into three groups based on the degree of cleavage between the hemispheres (Cohen, 2001). In alobar HPE, the forebrain forms a holospheric, univentricular brain: mental retardation is profound and survival beyond 1 year of age is exceptional. In semilobar HPE, the telencephalon remains rostrally unpaired, whereas the posterior part of the interhemispheric fissure is present. In lobar HPE, pairing is almost complete with respect to the midline interhemispheric fissure. Although they can exist as isolated anomalies unrelated to HPE, arhinencephaly and agenesis of the septum pellucidum also belong to the HPE spectrum. Long survival is possible with semilobar and lobar HPE, but often associated with moderate to severe mental impairment and early onset seizures (Pineda-Alvarez et al., 2010).

HPE has complex etiology. In many cases, it appears to be the consequence of a genetic or an environmental disruption of the sonic hedgehog (SHH) signaling pathway, which is responsible of the specification of the neural tube but also plays a role in the proliferation of neural progenitors in the ventricular zone of the telencephalon. HPE is classically associated with several chromosome imbalance, including trisomy 13, which is the most common

Table 13.3

Common DNA repair deficiency syndromes associated with microcephaly

Syndrome	Gene	Inheritance	Neurological features*	Hematological and immunological defects	Other features	OMIM
Nijmegen breakage syndrome	*NBS1*	AR	Normal IQ (or mild MR)	Immunodeficiency, cancer predisposition	Growth delay, craniofacial dysmorphism (microgenia, 'bird-like' facies)	251260
LIG4 syndrome	*LIG4*	AR	Developmental delay (MR)	Immunodeficiency, pancytopenia, lymphoma	Growth delay, facial features similar to NBS, skin anomalies	606593
Severe combined immunodeficiency (SCID) with microcephaly, growth retardation and sensitivity to ionizing radiation	*NHEJ1*	AR	MR	SCID–recurrent infections with opportunistic organisms, lymphopenia, agammaglobulinemia	Growth retardation, dysmorphism	611291
Fanconi anemia	*FANC A-N*	AR	MR	Anemia, cancer predisposition, myelodysplasia, leukemia	Heart, kidney and limb malformations, skin pigmentation changes, low birth weight, short stature	227650, 300514, 227645, 605724, 227646, 600901, 603467, 602956, 609053, 609054, 608111, 609644, 610832
Seckel syndrome	*ATR, CEP152, CENPJ, CEP63, ATRIP, NIN*	AR	MR, seizures, cerebellar vermis hypoplasia, pachygyria, hyperactivity	Pancytopenia	• Pre/postnatal growth retardation, dwarfism, craniofacial dysmorphism ("bird-like" facies)	210600
Microcephalic osteodysplastic primordial dwarfism type 2 (MOPD2)	*PCNT*	AR	MR Moyamoya disease, multiple aneurysms and infarcts	-	• Dwarfism, craniofacial dysmorphixsm, bone dysplasia, type II diabetes, café-au-lait spots	210720

Continued

Table 13.3

Continued

Syndrome	Gene	Inheritance	Neurological features*	Hematological and immunological defects	Other features	OMIM
Cockayne syndrome	*ERCC6/8*	AR	MR neurodegeneration	-	• "Cachectic" dwarfism, • Progressive pigmentary retinopathy, sensineural deafness, cutaneous photosensitivity, thin/dry hair, progeroid appearance, contractures	216400, 133540
Xeroderma pigmentosum	*ERCC1-5, XPA/C, DDB2*	AR	MR, hyporeflexia, spasticity, ataxia, choreoathetosis	Skin cancer predisposition	• Ichthyosis, photosensitivity, short stature, deafness	126380, 278700, 610651, 278720, 278730, 278740, 278760, 278780
Photosensitive trichothiodystrophy	*ERCC2/3*	AR	MR	Hypogammaglobulinemia	• Ichthyosis, photosensitivity, cataract, brittle hair and nails	126340, 133510

*Other than microcephaly.

Abbreviations: *NBS1*, Nibrin; *LIG4*, ATP-dependent DNA ligase IV; *NHEJ1*, nonhomologous end-joining factor 1; *FANC A-N*, Fanconi anemia complementation group A-N; *ATR*, ataxia-telangiectasia and RAD3-related protein; *PCNT*, pericentrin 2; *ERCC*, excision-repair cross-complementing protein; *XP*, xeroderma pigmentosum complementation group; *DDB2*, DNA damage-binding protein 2; MR, mental retardation; AR, autosomal recessive.

etiology. Point mutations or small deletions have been reported in *SHH*, *ZIC2*, *SIX3*, *TGIF, PTCH1*, and *GLI2* (Bendavid et al., 2010; Roessler and Muenke, 2010). Maternal diabetes is an environmental cause of HPE.

Microcephaly and brainstem/cerebellar malformation

Primary or congenital microcephaly may be associated with abnormalities of the posterior fossa, which may remain unnoticed in the prenatal assessment. Such brainstem and cerebellar malformations can worsen the prognosis of a child with microcephaly. Severe congenital microcephaly associated with polymicrogyria, corpus callosum agenesis, and cerebellar hypoplasia has been reported in a family where a homozygous balanced translocation silenced the *EOMES* gene by positional effect (Baala et al., 2007). Mutation of the X-linked calcium/calmodulin-dependent serine protein kinase (*CASK*) gene results in several phenotypes. The most severe mutations result in microcephaly with optic atrophy and severe hypoplasia of the brainstem and cerebellum in heterozygous females (Najm et al., 2008). Survival has exceptionally been reported in males. Hypomorphic mutations in *CASK* lead to X-linked mental retardation with congenital nystagmus (see Table 13.4).

Table 13.4

Microcephaly and brainstem/cerebellar malformations

Gene	Disease	Inheritance	Neurological phenotype*	Neuroradiological phenotype	OMIM
EOMES	–		Hypotonia, severe motor delay, early lethality (chronic infections)	Bilateral polymicrogyria, CCA, cerebellar hypoplasia	604615
CASK	Mental retardation and microcephaly with pontine and cerebellar hypoplasia	XR	Seizures, optic nerve hypoplasia, early death in males, severe MR in females	Simplified gyral pattern, thin brainstem with flattening of the pons, severe cerebellar hypoplasia	300172
TUBA1A	Lissencephaly 3	AD	Diplegia, tetraplegia, severe MR, epilepsy, delayed motor development	Lissencephaly, bilateral perisylvian pachygyria or agyria, subcortical heterotopias, dysmorphic basal ganglia, CCA, cerebellar hypoplasia, brainstem anomalies	602529
TUBB2B	Asymmetric polymicrogyria	AD	Tetraplegia/ hemiparesis, severe MR, epilepsy	Asymmetric polymicrogyria, cortical dyplasia, CCA, dysmorphic basal ganglia, cerebellar hypoplasia, brainstem anomalies	612850

*Other than microcephaly.

Abbreviations: *CASK*, calcium/calmodulin-dependent serine protein kinase; *TUBA1A*, alpha tubulin 1A; *TUBB2B*, beta tubulin 2B; CCA, corpus callosum agenesis; MR, mental retardation; AR, autosomal recessive; AD, autosomal dominant; XR, X-related disorders.

Mutations in the tubulin genes (effectors regulating cytoskeleton dynamics) can also be responsible for microcephaly with brainstem/cerebellar hypoplasia (see Table 13.4).

METABOLIC MICROCEPHALIES

Two specific forms, commonly associated with primary microcephaly, deserve specific special comments.

Serine deficiency disorders are a group of neurometabolic diseases caused by defects in the biosynthesis of L-serine, a precursor of metabolites such as nucleotides, phospholipids, and the neurotransmitters glycine and D-serine. Clinical manifestations include congenital microcephaly, seizures, severe pyramidal syndrome, and severe psychomotor retardation. The diagnosis of serine deficiency is based on the detection of low concentrations of serine and glycine in fasted plasma and, preferably, in cerebrospinal fluid (CSF). It may result from at least three different enzyme defects: 3-phosphoglycerate dehydrogenase deficiency (which leads to intractable seizures), 3-phosphoserine phosphatase, and phosphoserine aminotransferase deficiencies (Tabatabaie et al., 2010). Serine deficiency is potentially treatable with supplementation of L-serine, sometimes combined with glycine.

Amish microcephaly is a recessive disorder characterized by severe congenital microcephaly and alpha-ketoglutaric aciduria, usually lethal during the first year of life. All patients reported so far come from the Amish community and carry a homozygous p.Gly177Ala mutation in the *SLC25A19* gene (Rosenberg et al., 2002), coding for a thiamine pyrophosphate transporter (previously supposed to be the mitochondrial deoxyribonucleotide carrier DNC), leading to decreased activity of the three mitochondrial enzymes that require thiamine pyrophosphate as a cofactor: pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and branched chain amino acid dehydrogenase. Lissencephaly, vermis hypoplasia, and dysgenesis of the corpus callosum may be associated.

SECONDARY MICROCEPHALIES

Microcephaly that occurs postnatally within the first years of life (normal OFC at birth) often implies ongoing neurodegeneration and/or death of other cells. Most forms of secondary microcephaly such as those occurring in patients with Rett syndrome, Aicardi-Goutières disease, infantile neuronal ceroid lipofuscinoses, or other metabolic diseases are addressed in other chapters. Patients with secondary microcephaly often show progressive motor and cognitive deterioration and seizures, but their symptoms may also appear as nonprogressive. For example, hypotonia, feeding difficulties and progressive microcephaly in the first year of life were reported in boys with the X-linked-specific thyroid hormone cell transporter deficiency (*MCT8*) (Friesema et al., 2004). Primary microcephalies such as MCPH may sometimes mimic secondary microcephalies, as OFC can still be low – normal at birth and falls below –3 SD only in the first year of life.

SYNDROMIC MICROCEPHALIES

A large number of syndromes are associated with microcephaly, which can either be a major handle for suggesting or confirming the diagnosis, or a secondary, nonmandatory feature (Abuelo, 2007). More than 700 clinical syndromes are recorded with microcephaly in the London Dysmorphology Database and OMIM. Typically, most autosomal chromosomal anomalies are associated with small head size, as in classical 4p16 deletion (Wolff – Hirshhorn syndrome), but also in more recently delineated entities such as 1p36 deletion (Battaglia et al., 2008) and 1q21.1 microdeletion (Brunetti-Pierri et al., 2008). Table 13.5 presents a selected group of disorders of known etiology, in which microcephaly is a key feature.

MANAGEMENT OF MICROCEPHALY

Proper evaluation of a microcephalic child should be done by a pediatric neurologist and a dysmorphologist. A comprehensive anamnesis, including prenatal history, postnatal medical and developmental steps, and familial history with three-generational pedigree should be collected. Growth charts for height and OFC and a detailed physical examination should be recorded in all cases. They will sometimes suggest a specific diagnosis or deliver handles for further testings. Genetic etiologies have been reported in 15% to 50% of patients with isolated or syndromal microcephalies. The prevalence of metabolic disorders is estimated to be 1%. Children with true microcephaly are more likely to have imaging abnormalities and more severe developmental impairments than those with milder microcephaly. Comorbidities include epilepsy (40%), cerebral palsy (20%), mental retardation (50%), and ophthalmologic disorders (20% to 50%). MRI neuroimaging is useful in all cases: the yield of neuroimaging ranges from 40% (in mild microcephalies) to 80% (in the most severe forms) (Fig. 13.1). Molecular karyotype by high resolution CGH-array or SNP-array, should be performed in all cases where an acquired etiology is not perfectly demonstrated. Screening for undiagnosed or "forgotten" maternal hyperphenylalaninemia should be considered when no sibs with normal OFC exist. Specific testing may be considered based on associated abnormalities suggesting a specific diagnosis. Screening for coexistent conditions such as cerebral palsy,

Table 13.5

Syndromal microcephalies with known etiologies

Chromosomal/genomic microcephalies	Inheritance	Genetic/genomic anomaly	Key signs
1q43-q44 deletion syndrome	Chromosomal	Submicroscopic deletion	Growth retardation, dysmorphic features (hypertelorism, depressed nasal bridge), congenital heart defects
4p deletion (Wolff–Hirshhorn) syndrome	Chromosomal	WHSC1 and WHSC2: 2 nonoverlapping regions of chromosome 4 which lead to 4p- phenotype	IUGR. Typical dysmorphism: hypertelorism, prominent glabella, giving a Greek helmet appearance, broad nasal tip, bilateral cleft lip, short philtrum, microcephaly, large ears
5p deletion syndrome (cri-du-chat)	Chromosomal	Continuous gene deletion syndrome	Hypertelorism, round face. Typical high pitched voice
7q11 deletion (Williams syndrome)	Chromosomal	NHAR-mediated deletion	Short stature, hypertelorism, short, upturned nose, long philtrum, everted lower lip, aortic stenosis, specific, infantile hypercalcemia, overfriendly personality
22q11 syndrome (DiGeorge syndrome/ velocardiofacial syndrome)	Chromosomal	NHAR-mediated deletion	Cleft palate, congenital heart defect (mainly, but not exclusively), conotruncal, abnormal nose shape (broad base, bulbous tip, parallel edges, velar insufficiency)
1q21.1 microdeletion syndrome	Chromosomal	NHAR-mediated deletion	Microcephaly (2/3), congenital heart abnormality (1/3), ligamentous laxity, or joint hypermobility, hypotonia (5/21), seizures (3/21) NB: Incomplete penetrance: the deletion can be found in normally developed or borderline carrier parent
1p36 microdeletion	Chromosomal	Deletion of variable size in the sus-subtelomeric 1p region	Microcephaly, brachycephaly (18/30 or 60%), frontal bossing, deep-set eyes, straight eyebrows, narrow palpebral fissures, flat nose, and pointed chin. Heart defect
17p11 microdeletion (Miller – Dieker syndrome)	Chromosomal autosomal dominant	Terminal deletion of variable size	Typical lissencephaly type 1 with PAHAH1B1 mutation. Associated with dysmorphic traits if deletion involves YWHAE

Continued

Table 13.5

Continued

Chromosomal/genomic microcephalies	Inheritance	Genetic/genomic anomaly	Key signs
Monogenic syndromes			
Renpenning syndrome (X-linked microcephaly)	X-linked	*PQBP1* (polyglutamine tract binding protein 1 gene)	Microcephaly, long narrow face, short stature with lean body build, coloboma and other eye defects, stiff thumbs, small testes NB: PQBP1 mutation is also associated with nonsyndromic mental retardation
Feingold syndrome	AD	*MYCN*	Microcephaly–often with normal intelligence -, multiple digestive atresias (esophagus, duodenum), brachymesophalangy of the 5th fingers, 4–5 syndactyly of the toes and short palpebral fissures
Cohen syndrome	AR	*COH1*	Microcephaly, truncular obesity, mental retardation, low muscle tone, narrow hands and feet, and distinctive facial features with prominent upper central teeth, retinitis pigmentosa, and leucopenia
Rubinstein–Taybi syndrome	AD or chromosomal	*CREBP* mutation or microdeletion *EP300*	Microcephaly, mental retardation, short stature, broad deviated thumbs and great toes (not with EP300 mutations), and characteristic facial features (antimongoloid eye slant, hypertelorism, and a convex nose with the columella protruding below the alae nasi). Sometimes: agenesis of the corpus callosum
Rett syndrome	X-linked, dominant	*MECP2*	Girls with normal pre- and perinatal history, normal development and head circumference up to 6 months of age, subsequent regression of social and motor skills, hand-wringing or clapping with frequent mouthing, and truncal and gait ataxia, epilepsy, alternating bouts of polypnea and apnea
Rett variants with early epilepsy	X-linked dominant	*CDKL5/STK9*	Girls with a severe form of Rett with severe epilepsy onset before 6 months of age

Continued

Table 13.5

Continued

Chromosomal/genomic microcephalies	Inheritance	Genetic/genomic anomaly	Key signs
Congenital Rett syndrome	Autosomal dominant	*FOXG1* *MEF2C*	Boys and girls with early onset, severe encephalopathy and Rett-like stereotypic movements, epilepsy, and cerebral malformations
Mowat–Wilson syndrome	Autosomal dominant	*ZEB2* (or *ZFHX1B* or *SIP1*)	Postnatal microcephaly, Hirschsprung disease or constipation, facial dysmorphism: deep-set, large eyes, a broad low nasal bridge, prominent columella, an open mouthed expression, prominent chin, and large uplifted, fleshy ear lobules. Agenesis of the corpus callosum
Smith–Lemli–Opitz syndrome	AR	7-dehydro-cholesterol-delta-7 reductase deficiency	Microcephaly, ptosis, bi-temporal narrowing, anteverted nostrils, broad nasal tip, micrognathia, cleft palate, visceral anomalies, hypospadias, toe 2−3 syndactyly, postaxial polydactyly. High 7OH-cholesterol in serum. May be observed with HPE
Cornelia De Lange syndrome	AD X-linked	*NIPBL, RAD21, HDAC8, SMC3, SMC1A*	IUGR, postnatal short stature, microcephaly, limb reduction defect, hirsutism, facial dysmorphism (synophrys, hairy forehead, long eyelashes, short nose, anteverted, flared nostrils, long philtrum and a thin upper lip). Marked variability with severe and mild cases with normal growth and OFC X-linked variant: milder form, no limb anomalies. Female carriers may express the phenotype

Some emblematic microcephaly syndromes. The syndromes associated with DNA repair defect are listed separately in Table 13.3. IUGR, intra-uterine growth retardation; NHAR, nonhomologous allelic recombination: faulty recombination between highly similar loci (duplicons) located at relatively short distance one from another.
Common mechanisms for recurrent microrearrangements.

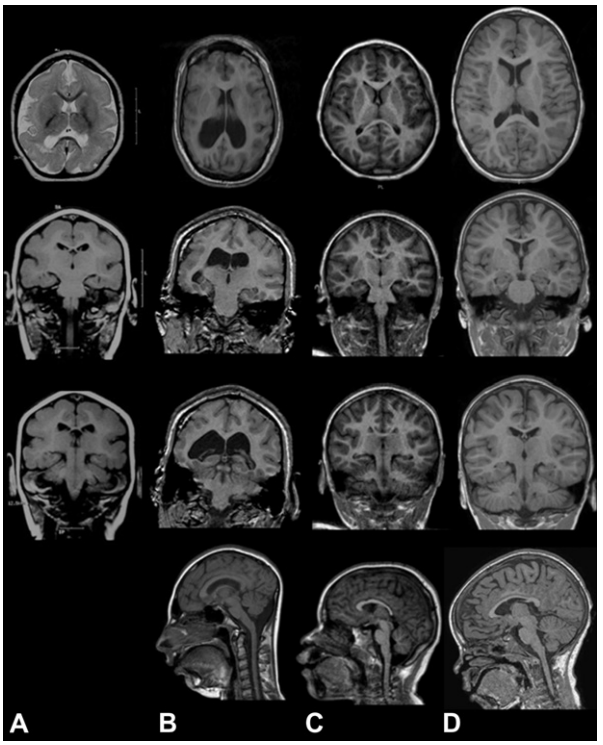

Fig. 13.1. MRI findings from patients exhibiting microcephaly caused by (**A**) *WDR62* (from Nicholas et al., 2011); (**B**) *ASPM* mutation, and **(C)** 1q43-q44 microdeletion syndrome compared to (**D**) control subject (from Passemard et al., 2009b). Axial, coronal, and sagittal magnetic resonance images confirm the clinical diagnosis of microcephaly, with distinct presentation depending on the molecular diagnosis: pachygyria and impressive gyral simplification close to microlissencephaly due to *WDR62* mutation (A) unilateral, polymicrogyria and gyral simplification associated with *ASPM* mutation and microcephaly with more preserved gyration in patient C with 1q43q44 microdeletion.

epilepsy, and sensory deficits may also be considered, including fundus examination (Ashwal et al., 2009).

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