治療・予後

発作は難治で，約70%の症例では毎日発作がみられる．神経学的には，歩行可能例は10～20%，有意語表出例は10%前後である．

主要な鑑別診断

- 線状皮膚欠損を伴う小眼球症
- 胎内感染症(TORCH)
- チュブリン病(*TUBA8*，*TUBB2B*，*TUBB3*，*TUBB*の各変異)

文献

1) Aicardi J: Aicardi syndrome. Brain Dev 27: 164-171, 2005
2) Barkovich AJ, et al: A developmental and genetic classification for malformations of cortical development: update 2012. Brain 135: 1348-1369, 2012
3) Hopkins B, et al: Neuroimaging aspects of Aicardi syndrome. Am J Med Genet A 146A: 2871-2878, 2008

(加藤光広)

2 Miller-Dieker症候群

疫学

Miller-Dieker(ミラー・ディーカー)症候群は，8の字型の完全な無脳回と特異的な顔貌異常を呈する古典型滑脳症の最重症型であり，17p13.3領域の*LIS1*からYWHAE(14-3-3ε)までの遺伝子群の欠失が原因である．*LIS1*や*DCX*単独の変異ではさまざまな程度の古典型滑脳症を示すが，顔貌異常を認めず，Miller-Dieker症候群とは区別される[1]．1997年の全国疫学調査では広汎性滑脳症が61例報告されているが，隣接遺伝子症候群としての本症はさらに少ないと考えられる．性差はない．乳児期から哺乳障害や低緊張による発達遅滞，てんかん性スパズムで発症する．新生突然変異が原因であり，基本的には孤発性だが，片親の均衡型転座や生殖細胞モザイクの場合は同胞発症もありうる．

国際分類の中の位置づけ

1989年のILAE分類では症候性に，2009年の分類では構造的/代謝性に分類される．2012年の皮質形成異常の分類では，神経細胞移動異常症の後頭優位型滑脳症に分類される[2]．

臨床症状

点頭てんかんの併発が多い．身体所見として広い前額，前額正中から眉間にかけての膨隆と陥凹，側頭部の陥凹，耳介低位，小さく短い鼻，上向きの鼻孔，薄い口唇，小顎などの特異顔貌と後天性の小頭が認められる．時に心臓・腸管・腎臓・指趾など他の奇形を伴う．神経学的には低緊張が強い．

検査

脳波はてんかん性スパズムの出現に一致してヒプサリズミアを認める．そのほか広汎性の高振幅速波が特徴的である．画像は8の字形の典型的な完全無脳回(グレード1)を示し，皮質は10～20 mmに肥厚している(図11-33)．基底核には異常を認めない．*DCX*変異によるグレード1の無脳回は，画像による鑑別は難しいが，男児のみで特異顔貌を伴わない点が異なる．病理学的に大脳皮質は，脳表から①分子層，②表在細胞層，③細胞希薄層，④深部細胞層の4層構造を示す[3]．染色体検査では，fluorescence *in situ* hybridization(FISH)法で，*LIS1*を含む17p13.3領域の微細欠失が認められる．顔貌異常がはっきりせず単独の古典型滑脳症との鑑別が困難な場合は*LIS1*，*DCX*，*TUBA1A*などの遺伝子解析が必要である．

治療・予後

重度の精神運動発達遅滞と摂食障害を呈し，てんかん発作も難治である．心奇形など内臓奇形を伴うことも多く，呼吸や栄養など全身管理が必要である．肺炎を繰り返し，生命予後は不良である．

frontiers in Neuroscience

REVIEW
published: 21 May 2015
doi: 10.3389/fnins.2015.00181

Genotype-phenotype correlation in neuronal migration disorders and cortical dysplasias

Mitsuhiro Kato *†

Department of Pediatrics, Yamagata University Faculty of Medicine, Yamagata, Japan

Neuronal migration disorders are human (or animal) diseases that result from a disruption in the normal movement of neurons from their original birth site to their final destination during early development. As a consequence, the neurons remain somewhere along their migratory route, their location depending on the pathological mechanism and its severity. The neurons form characteristic abnormalities, which are morphologically classified into several types, such as lissencephaly, heterotopia, and cobblestone dysplasia. Polymicrogyria is classified as a group of malformations that appear secondary to post-migration development; however, recent findings of the underlying molecular mechanisms reveal overlapping processes in the neuronal migration and post-migration development stages. Mutations of many genes are involved in neuronal migration disorders, such as *LIS1* and *DCX* in classical lissencephaly spectrum, *TUBA1A* in microlissencephaly with agenesis of the corpus callosum, and *RELN* and *VLDLR* in lissencephaly with cerebellar hypoplasia. *ARX* is of particular interest from basic and clinical perspectives because it is critically involved in tangential migration of GABAergic interneurons in the forebrain and its mutations cause a variety of phenotypes ranging from hydranencephaly or lissencephaly to early-onset epileptic encephalopathies, including Ohtahara syndrome and infantile spasms or intellectual disability with no brain malformations. The recent advances in gene and genome analysis technologies will enable the genetic basis of neuronal migration disorders to be unraveled, which, in turn, will facilitate genotype-phenotype correlations to be determined.

Keywords: lissencephaly, heterotopia, polymicrogyria, tubulinopathy, interneuronopathy, *LIS1, DCX, ARX*

OPEN ACCESS

Edited by:
Chiaki Ohtaka-Maruyama, Tokyo Metropolitan Institute of Medical Science, Japan

Reviewed by:
Brian Key, Asdasdasd, Austria
Masaharu Hayashi, Tokyo Metropolitan Institute of Medical Science, Japan

***Correspondence:**
Mitsuhiro Kato, Department of Pediatrics, Yamagata University Faculty of Medicine, 2-2-2 Iida-nishi, Yamagata 990-9585, Japan
ktmt-hro@umin.ac.jp

†Present Address:
Mitsuhiro Kato, Department of Pediatrics, Showa University School of Medicine, Tokyo, Japan

Specialty section:
This article was submitted to Neurogenesis, a section of the journal Frontiers in Neuroscience

Received: *01 December 2014*
Accepted: *06 May 2015*
Published: *21 May 2015*

Citation:
Kato M (2015) Genotype-phenotype correlation in neuronal migration disorders and cortical dysplasias. Front. Neurosci. 9:181. doi: 10.3389/fnins.2015.00181

Introduction

The characteristic six-layered neocortex in the human brain is formed by two types of neuron, projection neurons and interneurons, which migrate from their birth places, such as the ventricular zone and ganglionic eminence, respectively. Neuronal migration disorders are human (or animal) diseases that result from the disruption of normal movement of neurons from their original birth site to their final destination during early development. As a consequence, the neurons remain somewhere along their migratory route, their location depending on the pathological mechanism and its severity. Many genes have been found to be responsible for neuronal migration disorders, such as *LIS1* and *DCX* in classical lissencephaly spectrum, *TUBA1A* in lissencephaly with cerebellar hypoplasia, *ARX* in X-linked lissencephaly with abnormal genitalia (XLAG), *FLNA* and *ARGEF2* in periventricular heterotopia, *FCMD* and glycosylation-related

genes, such as *POMT1*, *POMT2*, *POMGNT1*, *POMGNT2*, *FKRP*, *LARGE*, *TMEM5*, *POMK*, *ISPD*, *GMPPB*, *B3GNT1*, and *B3GALNT2* in cobblestone dysplasias, *GPR56*, *SRPX2*, and some tubulin-related genes, e.g., *TUBA8*, *TUBB2B*, and *TUBB3*, in polymicrogyria (Kato and Dobyns, 2003; Vuillaumier-Barrot et al., 2012; Buysse et al., 2013; Stevens et al., 2013; Fry et al., 2014). Recently, we found that mutations in *COL4A1*, which encodes type IV collagen alpha 1 subunit, cause schizencephaly accompanied by polymicrogyria in the adjacent cortex of the transmantle cleft as well as focal cortical dysplasia (Yoneda et al., 2013). Historically, brain malformations including neuronal migration disorders have been classified based on a postmortem examination. The advancement and spread of neuroimaging techniques, particularly magnetic resonance imaging (MRI), make it easier to find out many types of brain malformations, but make it more complicated to classify them. Moreover, the unveiling of responsible genes for brain malformations has changed the classification scheme and causes most neuroscientists and even physicians trouble to follow it. Here, I review the clinical manifestation of neuronal migration disorders, focusing mainly on lissencephaly, in terms of genotype-phenotype correlations.

Lissencephaly Spectrum: Classical Lissencephaly to Subcortical Band Heterotopia

Lissencephaly is classified as a spectrum of disorders caused by widespread abnormal transmantle migration, ranging from classical lissencephaly (agyria or pachygyria) to subcortical band heterotopia or double-cortex syndrome (Barkovich et al., 2012). Classical lissencephaly is characterized by a smooth (*lissos* in Greek) brain surface with a decreased number of sulci and wide gyri. Mutations in *LIS1*, located on chromosome 17p13.3, or *DCX* on Xq23 are the main cause for classical lissencephaly (**Table 1**) (Kato and Dobyns, 2003). Mutations in *DCX* are causative for classical lissencephaly in male individuals and subcortical band heterotopia in female individuals. A combination of a severity grading scale [the most severe form, Grade 1 (total agyria) to the mildest form, Grade 6 (subcortical band heterotopia) via the intermediate forms comprised of a combination of agyria, pachygyria, and subcortical band heterotopia] and an anterior or posterior gradient scale is useful to predict the causative gene for lissencephaly spectrum (Kato and Dobyns, 2003). For instance, mutations of *LIS1*, *ARX*, or *TUBA1A* result in a posterior more severe than anterior gradient, while mutations of *DCX* or *RELN* lead to an anterior more severe than posterior gradient. LIS1 participates in cytoplasmic dynein-mediated nucleokinesis, somal translocation, and cell motility (Smith et al., 2000) as well as mitosis or neurogenesis and chromosomal segregation (Faulkner et al., 2000). DCX is a microtubule-associated protein and is involved in microtubule polymerization and stabilization (Gleeson et al., 1999). Missense mutations in *DCX* responsible for lissencephaly spectrum are mainly located in two tandem repeats (N-terminal or C-terminal doublecortin domains), which bind to microtubules or free tubulin and other components (Friocourt et al., 2005), respectively.

MRI of the brain is useful to discriminate agyria, pachygyria, and subcortical band heterotopia. Agyria is generally characterized by the disappearance of deep sulci in more than one lobe and the thickness of the cortex is 10–20 mm (**Figure 1**). The gyri in pachygyria are wider than in the normal cortex and the thickness of the cortex is 4–9 mm (**Figure 2**). Brain MRI of subcortical band heterotopia shows bilateral continuous symmetric bands of gray matter underlying an almost normal cortical mantle with relatively shallow sulci (**Figure 3**). More than 90% of patients with subcortical band heterotopia are female and the cause is usually heterozygous *DCX* mutation. Subcortical band heterotopia in male patients is caused by somatic mosaic *DCX* mutations or *LIS1* mutations (Gleeson et al., 2000; Kato et al., 2001; D'agostino et al., 2002; Poolos et al., 2002). Coexistence of agyria and pachygyria or pachygyria and subcortical band heterotopia can be seen in the same patient, suggesting common mechanisms for these phenotypes. Microscopically, agyria and pachygyria present a four-layered cortex with an outer molecular layer, superficial layer, cell sparse layer, and deep cellular layer. In the marginal zone between pachygyria and subcortical band heterotopia, the outer molecular layer corresponds to layer I of the normal six-layered cortex, the superficial layer corresponds to layers II–VI, the cell sparse layer corresponds to subcortical white matter, and the deep cellular layer corresponds to band heterotopia with a mass of unlayered ectopic neurons (**Figure 4**). The primary pathology of lissencephaly due to the *DCX* mutations shows only minor differences compared with that caused by *LIS1* mutations, for example, inferior olivary ectopia is present in *LIS1* mutation brains but is absent in *DCX* mutation brain (Berg et al., 1998); however, Viot et al. report a different cortical architecture for *DCX* lissencephaly (Viot et al., 2004).

The severity of the clinical manifestations of lissencephaly spectrum is correlated with the degree of brain malformation. Patients with agyria show severe muscle hypotonia from infancy (known as floppy infant) and achieve neither head control nor are they able to say meaningful words. A specific form of epileptic seizure, epileptic spasms, occurs in 80% of patients with agyria or pachygyria, although electroencephalography (EEG) may not present with typical hypsarrhythmia, which is characteristically seen in infantile spasms or West syndrome (Guerrini, 2005). However, the main clinical features of subcortical band heterotopia are intellectual disability and epileptic seizures, both of which are milder than those of agyria or pachygyria. Intellectual disability ranges from normal to severe retardation and correlates with the thickness of the band and the degree of pachygyria (Barkovich et al., 1994; Bahi-Buisson et al., 2013). Genetic counseling is particularly important for parents that have a boy with classical lissencephaly or a girl with subcortical band heterotopia because the mother may be a heterozygous carrier of the *DCX* mutation.

Miller-Dieker syndrome is a contiguous gene syndrome caused by a microdeletion in 17p13.3, a region that contains *LIS1* and *YWHAE* (which encodes 14-3-3 protein epsilon). Phenotypes of Miller-Dieker syndrome are more severe than

TABLE 1 | Clinical features of gene mutations causing cortical disruptions.

Gene	Locus	Inheritance mode	LIS	HET	PMG	MIC at birth	ACC	PCH	Brain	Other findings
LIS1~YWHAE	17p13.3	AD	+						Total agyria (Figure-of-8 appearance)	Characteristic face and MCA
LIS1	17p13.3	AD	+	+, rare					Agyria to subcortical band HET, mainly pachygyria in anterior and agyria in posterior	
DCX (male)	Xq23	XL	+	+					LIS. Subcortical band HET due to somatic mosaic mutation.	
DCX (female)	Xq23	XL	+, rare	+					Subcortical band HET	
TUBA1A	12q13.12	AD	+	+, rare	+, rare	+	+	+	MIC, agyria to subcortical band HET, PMG, PCH, ACC	
TUBA8	22q11	AR			+		+		PMG, agenesis or hypogenesis of the corpus callosum, dysmorphic brainstem	Optic nerve hypoplasia
TUBB2A	6p25.2	AD						+	Mild PCH	
TUBB2B	6p25.2	AD			+	+		+	MIC, PMG, dysmorphic basal ganglia, PCH, dysmorphic brainstema	CFEOM
TUBB3	16q24.3	AD			+			+	PMG, gyral disorganization, dysmorphic basal ganglia, PCH	CFEOM
TUBB	6p21.33	AD		+	+	+	+		MIC, focal band HET or PMG, dysmorphic basal ganglia, abnormal corpus callosum	Microophthalmia
TUBG1	17q21.2	AD	+	+					Posterior dominant lissencephaly, dysmorphic corpus callosum	
ARX (male)	Xp22.13	XL	+				+		Posterior dominant LIS with ACC and dysmorphic basal ganglia	Hypoplastic genitalia, diarrhea
ARX (female)	Xp22.13	XL					+		ACC in half of the cases	
RELN	7q22.1	AR	+					+	Anterior dominant diffuse pachygyria with PCH	
VLDLR	9p24.2	AR	+					+	Diffuse pachygyria with PCH	
MCPH1	8p23.1					+			MIC	
WDR62	19q13.12	AR	+	+	+	+	+		MIC, pachygyria, PMG, or subcortical band HET, abnormal corpus callosum	
NDE1	16p13.11	AR				+	+		MIC, simplified gyral pattern, ACC	
COL4A1	13q34	AD, low penetrance							Porencephaly, schizencephaly, focal cortical dysplasia	Myopathy, hematuria, anemia

ACC, Agenesis of the corpus callosum; CFEOM, Congenital fibrosis of the extraocular muscle; HET, heterotopia; LIS, classical lissencephaly or agyria/pachygyria; MCA, multiple congenital anomalies; MIC, microcephaly; PCH, pontocerebellar hypolasia; PMG, polymicrogyria.

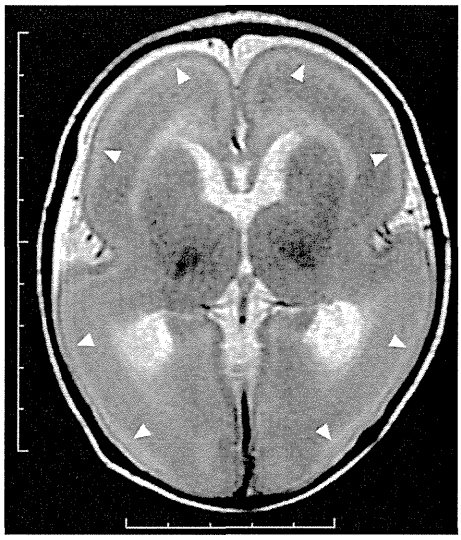

FIGURE 1 | Complete agyria in a *DCX* mutation patient (Grade 1 on the severity scale). T2-weighted axial MRI image. Wide shallow sylvian fissures create a figure-of-eight appearance. The thickness of the cortex is over 10 mm. A high-intensity (white) line (arrow heads) beneath the cerebral surface is consistent with a cell sparse layer of the four-layered cortex.

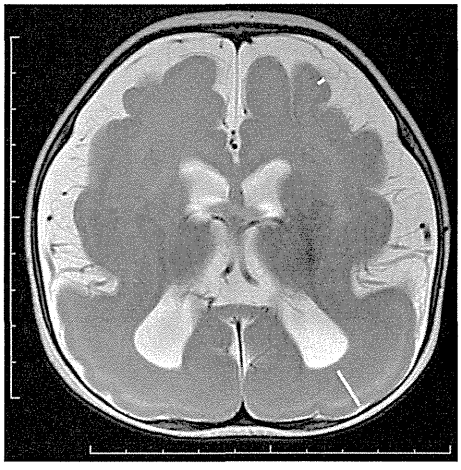

FIGURE 2 | Anterior pachygyria and posterior agyria in a *LIS1* mutation patient (Grade 3 on the severity scale). T2-weighted axial MRI image. Note the difference in the width of gyri, the depth of sulci and the thickness of the cortex (bars) between anterior and posterior regions.

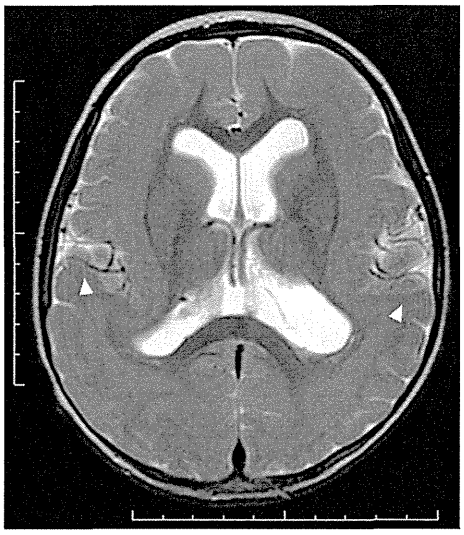

FIGURE 3 | Subcortical band heterotopia or double cortex syndrome in a *DCX* mutation patient (Grade 5 on the severity scale). T2-weighted axial MRI image. Subcortical heterotopic gray matter in the posterior region fuses into the pachygyric cortex in the anterior region (arrowheads).

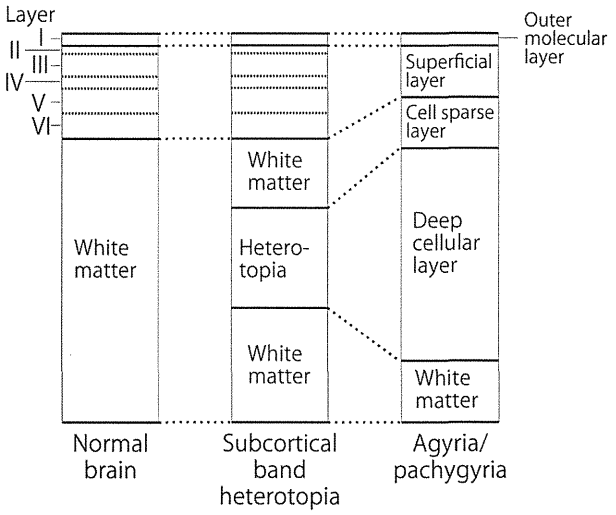

FIGURE 4 | Schematic diagram of cortical layers in the lissencephaly spectrum compared to the normal brain. Deep cellular layer of the pachygyric or agyric cortex fuses with laminar or band heterotopia in the subcortical white matter, but not with normal six-layered cortex.

that of classical lissencephaly because of an isolated *LIS1* mutation. They are characterized by complete agyria and facial abnormalities including prominent forehead, bitemporal hollowing, short nose with upturned nares, prominent upper lip with downturned vermilion border and small jaw, and sometimes other congenital defects involving the heart, kidneys, intestine, or fingers (Kato and Dobyns, 2003). Neurological findings of Miller–Dieker syndrome are similar to those of patients with agyria, such as severe developmental delay with weak muscle tone and profound intellectual disability, intractable seizures, dysphagia, and poor prognosis with recurrent infection of the respiratory system.

Tubulin-Related Disorders, Tubulinopathies

Microtubules provide the main structural framework for the shafts of axons and dendrites, and with actin serve as tracks for intracellular trafficking and to provide the driving force underlying neurite extension and intracellular movement of organelles during mitosis (Flynn et al., 2013). Recently, genes

involved in microtubule function have been identified to be causative for various human diseases, such as lissencephaly (Keays et al., 2007; Poirier et al., 2007), polymicrogyria (Abdollahi et al., 2009; Jaglin et al., 2009; Jansen et al., 2011), simplified gyral patter in which the cortical thickness is normal (Cushion et al., 2014), complex brain malformations (Poirier et al., 2010, 2013; Breuss et al., 2012), abnormal eye movement (Tischfield et al., 2010), torsion dystonia (Hersheson et al., 2013), and hypomyelinating leukodystrophy (Simons et al., 2013). All the above are classified as tubulinopathies (Cushion et al., 2013; Bahi-Buisson et al., 2014). Microtubules are assembled from soluble tubulin heterodimers consisting of alpha- and beta-tubulin. Multiple isoforms of both tubulins are encoded by different genes. Mutations of *TUBA1A*, which encodes alpha tubulin, cause lissencephaly spectrum, particularly diffuse agyria or perisylvian pachygyria, with microcephaly, agenesis of the corpus callosum, and cerebellar hypoplasia (**Figure 5**) (Bahi-Buisson et al., 2008). *TUBA1A* mutations account for only 1% of isolated classical lissencephaly; however, they account for approximately 30% of patients with lissencephaly associated with cerebellar hypoplasia (Kumar et al., 2010). Dysgenesis of the anterior limb of the internal capsule and disorganization of the hippocampus are other neuroimaging features for *TUBA1A* mutation (Poirier et al., 2007). Mutations of *TUBA1A* cause polymicrogyria as well. Interestingly, mutations of *TUBB2B* cause polymicrogyria with or without congenital fibrosis of the external ocular muscles as well as bilateral perisylvian pachygyria(Cederquist et al., 2012; Romaniello et al., 2014). Polymicrogyria is classified as a group of malformations that appear secondary to post-migration development; however, recent findings of the underlying molecular mechanisms reveal overlapping process in neuronal migration and post-migration development stages.

Mutations of *TUBA8* cause polymicrogyria with optic nerve hypoplasia and display autosomal recessive inheritance (Abdollahi et al., 2009). Mutations of *TUBB2A*, which encodes beta-tubulin, cause infantile-onset epilepsy with simplified gyral patterning (Cederquist et al., 2012; Cushion et al., 2014; Romaniello et al., 2014). Mutations of *TUBB3* cause two distinct forms. One is congenital fibrosis of the external ocular muscles or oculomotor nerve hypoplasia and later-onset peripheral axon degeneration with dysgenesis of the corpus callosum, anterior commissure, and internal capsule, but with no cortical dysplasia suggesting migrational defects (Tischfield et al., 2010). Another is cortical dysgenesis including polymicrogyria, pontocerebellar hypoplasia, and abnormal basal ganglia, but with no ocular motility defects (Poirier et al., 2010). The main mechanisms underlying the phenotypes caused by*TUBB3* mutations are impaired axon guidance owing to disrupted microtubule dynamics and kinesin interaction (Tischfield et al., 2010). Tubulinopathies caused by the mutations of the genes encoding alpha- or beta-tubulin demonstrate more extensive phenotypes compared to other gene mutations, such as *LIS1*, *DCX*, or *RELN*. Mutations of *TUBA1A*, which encodes alpha-tubulin 1A, is the most frequently found in patients with brain malformations, while more genes encoding beta-tubulin, such as *TUBB2A*, *TUBB2B*, *TUBB3*, *TUBB4A*, and *TUBB*, are identified in a wide spectrum of disorders besides brain malformations. Pathological mechanisms and discrepancy between alpha- and beta-tubulinopathies should be elucidated.

ARX-Related Disorders, Interneuronopathies

The embryonic cerebral cortex at the stage of neuronal migration contains neuronal cells with two modes of migration; radial migration from the ventricular zone toward the pia and tangential migration from ganglionic eminence along a tangential trajectory into the developing cortex. Radially

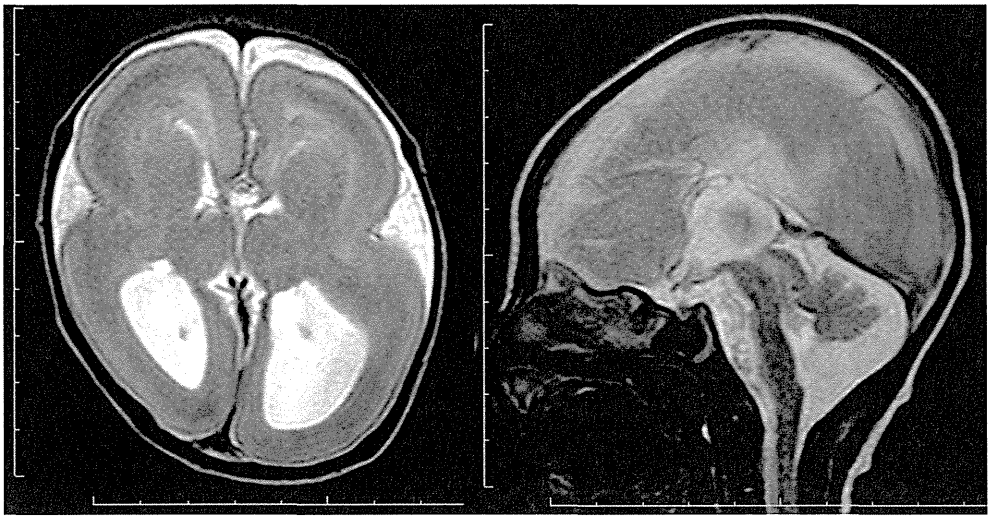

FIGURE 5 | Complete agyria in a *TUBA1A* mutation patient (Grade 1 on the severity scale). T2-weighted axial MRI image (left) and midsagittal image (right). The boundary of the caudate nucleus and lentiform nucleus is obscure. Complete agenesis of the corpus callosum and pontocerebellar hypoplasia are also seen.

migrating neurons in the cortex are mainly excitatory projection neurons expressing glutamate as a neurotransmitter. Tangentially migrating neurons are inhibitory interneurons expressing the neurotransmitter GABA. XLAG is caused by mutation of *ARX*, which is expressed in the embryonic ganglionic eminence, neocortex, and hippocampus and plays important roles in neuronal proliferation, interneuronal migration, and differentiation in the embryonic forebrain, as well as a secondary role in differentiation of the testes (Kitamura et al., 2002). Patients with XLAG present occipital-predominant classical lissencephaly, particularly anterior pachygyria and posterior agyria, or a simplified gyral pattern, agenesis of the corpus callosum, and abnormal basal ganglia (Kato et al., 2004). In the most severe form of XLAG, patients show hydranencephaly with a large occipital cavity. Female carriers of *ARX* mutations causing XLAG have a risk of agenesis of the corpus callosum with no cortical defects. Abnormalities of external genitalia range from hypoplastic penis or undescended testes to complete female appearance, while the karyotype is 46,XY. Neuropathological studies show a complete loss or a decreased number of cortical interneurons in human XLAG and in *Arx*-null mice (Bonneau et al., 2002; Kitamura et al., 2002) and a three-layered cortex in human XLAG (Forman et al., 2005). Patients with XLAG show intractable seizures soon after birth, suggesting a great disparity between excitatory projection neurons and inhibitory interneurons. *ARX* mutations in patients with XLAG are null mutations or non-conservative missense mutations at critical amino acids in the homeodomain, while other missense mutations or expansion mutations in the polyalanine tract result in X-linked intellectual disability with or without dystonia, West syndrome, Ohtahara syndrome, or early infantile epileptic encephalopathy with suppression burst on EEG but with no brain malformation (Bienvenu et al., 2002; Stromme et al., 2002; Guerrini et al., 2007; Kato et al., 2007, 2010). Interestingly, longer polyalanine expansion is correlated with more severe and earlier onset phenotypes. A wide spectrum of ARX-related disorders forms a group of interneuronopathies based on the role of ARX during neurogenesis, as seen in patients and in the *Arx*-null mouse model (Kato and Dobyns, 2005; Marsh et al., 2009).

Classical Lissencephalies Associated with Other Forms of Brain Malformation

Classical lissencephaly caused by *LIS1* or *DCX* mutations usually exist in isolated forms and only show cortical dysplasia on brain MRI. Rare variant forms of lissencephaly are associated with congenital microcephaly, cerebellar hypoplasia, or agenesis of the corpus callosum. Each form demonstrates characteristic radiological findings and some of the causative genes have been identified.

A lissencephaly group with cerebellar hypoplasia can be classified into several types according to brain imaging, additional clinical features, and causative genes (Ross et al., 2001). Among them, frontal predominant mild lissencephaly (diffuse pachygyria) with severe hippocampal and cerebellar hypoplasia or Reelin-type lissencephaly is caused by mutation of either *RELN* or *VLDLR* and shows autosomal recessive inheritance (Hong et al., 2000; Boycott et al., 2005). Dysequilibrium syndrome is an allelic disorder of the *VLDLR* locus (Moheb et al., 2008). Reelin-type lissencephaly has an inverted or no clear pattern of cortical lamination attributable to abnormal migration of the neurons in an outside-in birth order (Cooper, 2008; Dekimoto et al., 2010).

Lissencephaly can be associated with congenital microcephaly, though the head circumference of lissencephaly caused by the *LIS1* or *DCX* mutations is usually within the normal range. Lissencephaly with a head circumference of less than −3 SD at birth is classified as microlissencephaly (Barkovich et al., 2005) or microcephaly with lissencephaly (Barkovich et al., 2012). Although many genes identified to be responsible for primary microcephaly, such as *MCPH1*, *ASPM*, *CENPJ*, *CDK5RAP2*, and *PNKP*, are involved with the cell-cycle phase of mitosis affecting neurogenesis (Barbelanne and Tsang, 2014), the causative genes for microlissencephaly remain unknown in many cases. Mutations of *WDR62*, which encodes a protein localized to centrosomes throughout mitosis and nucleoli during interphase, cause microcephaly with pachygyria or polymicrogyria (Bilguvar et al., 2010). Mutations of *NDE1*, which encodes a protein that binds dynein and functions in centrosome duplication, as well as the *TUBA1A* mutations mentioned above, cause microcephaly with a simplified gyral pattern, agenesis of the corpus callosum, and cerebellar hypoplasia (Alkuraya et al., 2011; Bakircioglu et al., 2011).

Conclusion

Neuronal migration disorders are classified based on causative genes as well as on brain MRI and neuropathological findings. There are strong relationships between clinical manifestations and mutation of a particular gene, in accordance with the expression and functions of that gene. Recent advances in gene and genome analysis technology will enable the genetic basis of neuronal migration disorders to be readily determined, facilitating the elucidation of genotype-phenotype correlations.

Acknowledgments

The author is grateful to the patients and their families for their kind cooperation. This study was partially funded by the Ministry of Health, Labour and Welfare of Japan (26310301), and an Intramural Research Grant (24-7, 27-5) for Neurological and Psychiatric Disorders from the National Center of Neurology & Psychiatry. This study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Abdollahi, M. R., Morrison, E., Sirey, T., Molnar, Z., Hayward, B. E., Carr, I. M., et al. (2009). Mutation of the variant alpha-tubulin TUBA8 results in polymicrogyria with optic nerve hypoplasia. *Am. J. Hum. Genet.* 85, 737–744. doi: 10.1016/j.ajhg.2009.10.007

Alkuraya, F. S., Cai, X., Emery, C., Mochida, G. H., Al-Dosari, M. S., Felie, J. M., et al. (2011). Human mutations in NDE1 cause extreme microcephaly with lissencephaly [corrected]. *Am. J. Hum. Genet.* 88, 536–547. doi: 10.1016/j.ajhg.2011.04.003

Bahi-Buisson, N., Poirier, K., Boddaert, N., Saillour, Y., Castelnau, L., Philip, N., et al. (2008). Refinement of cortical dysgeneses spectrum associated with TUBA1A mutations. *J. Med. Genet.* 45, 647–653. doi: 10.1136/jmg.2008.058073

Bahi-Buisson, N., Poirier, K., Fourniol, F., Saillour, Y., Valence, S., Lebrun, N., et al. (2014). The wide spectrum of tubulinopathies: what are the key features for the diagnosis? *Brain* 137, 1676–1700. doi: 10.1093/brain/awu082

Bahi-Buisson, N., Souville, I., Fourniol, F. J., Toussaint, A., Moores, C. A., Houdusse, A., et al. (2013). New insights into genotype-phenotype correlations for the doublecortin-related lissencephaly spectrum. *Brain* 136, 223–244. doi: 10.1093/brain/aws323

Bakircioglu, M., Carvalho, O. P., Khurshid, M., Cox, J. J., Tuysuz, B., Barak, T., et al. (2011). The essential role of centrosomal NDE1 in human cerebral cortex neurogenesis. *Am. J. Hum. Genet.* 88, 523–535. doi: 10.1016/j.ajhg.2011.03.019

Barbelanne, M., and Tsang, W. Y. (2014). Molecular and cellular basis of autosomal recessive primary microcephaly. *Biomed Res. Int.* 2014:547986. doi: 10.1155/2014/547986

Barkovich, A. J., Guerrini, R., Battaglia, G., Kalifa, G., N'guyen, T., Parmeggiani, A., et al. (1994). Band heterotopia: correlation of outcome with magnetic resonance imaging parameters. *Ann. Neurol.* 36, 609–617. doi: 10.1002/ana.410360409

Barkovich, A. J., Guerrini, R., Kuzniecky, R. I., Jackson, G. D., and Dobyns, W. B. (2012). A developmental and genetic classification for malformations of cortical development: update 2012. *Brain* 135, 1348–1369. doi: 10.1093/brain/aws019

Barkovich, A. J., Kuzniecky, R. I., Jackson, G. D., Guerrini, R., and Dobyns, W. B. (2005). A developmental and genetic classification for malformations of cortical development. *Neurology* 65, 1873–1887. doi: 10.1212/01.wnl.0000183747.05269.2d

Berg, M. J., Schifitto, G., Powers, J. M., Martinez-Capolino, C., Fong, C. T., Myers, G. J., et al. (1998). X-linked female band heterotopia-male lissencephaly syndrome. *Neurology* 50, 1143–1146. doi: 10.1212/WNL.50.4.1143

Bienvenu, T., Poirier, K., Friocourt, G., Bahi, N., Beaumont, D., Fauchereau, F., et al. (2002). ARX, a novel Prd-class-homeobox gene highly expressed in the telencephalon, is mutated in X-linked mental retardation. *Hum. Mol. Genet.* 11, 981–991. doi: 10.1093/hmg/11.8.981

Bilguvar, K., Ozturk, A. K., Louvi, A., Kwan, K. Y., Choi, M., Tatli, B., et al. (2010). Whole-exome sequencing identifies recessive WDR62 mutations in severe brain malformations. *Nature* 467, 207–210. doi: 10.1038/nature09327

Bonneau, D., Toutain, A., Laquerriere, A., Marret, S., Saugier-Veber, P., Barthez, M. A., et al. (2002). X-linked lissencephaly with absent corpus callosum and ambiguous genitalia (XLAG): clinical, magnetic resonance imaging, and neuropathological findings. *Ann. Neurol.* 51, 340–349. doi: 10.1002/ana.10119

Boycott, K. M., Flavelle, S., Bureau, A., Glass, H. C., Fujiwara, T. M., Wirrell, E., et al. (2005). Homozygous deletion of the very low density lipoprotein receptor gene causes autosomal recessive cerebellar hypoplasia with cerebral gyral simplification. *Am. J. Hum. Genet.* 77, 477–483. doi: 10.1086/444400

Breuss, M., Heng, J. I., Poirier, K., Tian, G., Jaglin, X. H., Qu, Z., et al. (2012). Mutations in the beta-tubulin gene TUBB5 cause microcephaly with structural brain abnormalities. *Cell Rep.* 2, 1554–1562. doi: 10.1016/j.celrep.2012.11.017

Buysse, K., Riemersma, M., Powell, G., van Reeuwijk, J., Chitayat, D., Roscioli, T., et al. (2013). Missense mutations in beta-1,3-N-acetylglucosaminyltransferase 1 (B3GNT1) cause Walker-Warburg syndrome. *Hum. Mol. Genet.* 22, 1746–1754. doi: 10.1093/hmg/ddt021

Cederquist, G. Y., Luchniak, A., Tischfield, M. A., Peeva, M., Song, Y., Menezes, M. P., et al. (2012). An inherited TUBB2B mutation alters a kinesin-binding site and causes polymicrogyria, CFEOM and axon dysinnervation. *Hum. Mol. Genet.* 21, 5484–5499. doi: 10.1093/hmg/dds393

Cooper, J. A. (2008). A mechanism for inside-out lamination in the neocortex. *Trends Neurosci.* 31, 113–119. doi: 10.1016/j.tins.2007.12.003

Cushion, T. D., Dobyns, W. B., Mullins, J. G., Stoodley, N., Chung, S. K., Fry, A. E., et al. (2013). Overlapping cortical malformations and mutations in TUBB2B and TUBA1A. *Brain* 136, 536–548. doi: 10.1093/brain/aws338

Cushion, T. D., Paciorkowski, A. R., Pilz, D. T., Mullins, J. G., Seltzer, L. E., Marion, R. W., et al. (2014). *De novo* mutations in the beta-tubulin gene TUBB2A cause simplified gyral patterning and infantile-onset epilepsy. *Am. J. Hum. Genet.* 94, 634–641. doi: 10.1016/j.ajhg.2014.03.009

D'agostino, M. D., Bernasconi, A., Das, S., Bastos, A., Valerio, R. M., Palmini, A., et al. (2002). Subcortical band heterotopia (SBH) in males: clinical, imaging and genetic findings in comparison with females. *Brain* 125, 2507–2522. doi: 10.1093/brain/awf248

Dekimoto, H., Terashima, T., and Katsuyama, Y. (2010). Dispersion of the neurons expressing layer specific markers in the reeler brain. *Dev. Growth Differ.* 52, 181–193. doi: 10.1111/j.1440-169X.2009.01153.x

Faulkner, N. E., Dujardin, D. L., Tai, C. Y., Vaughan, K. T., O'connell, C. B., Wang, Y., et al. (2000). A role for the lissencephaly gene LIS1 in mitosis and cytoplasmic dynein function. *Nat. Cell Biol.* 2, 784–791. doi: 10.1038/35041020

Flynn, K. C., Stiess, M., and Bradke, F. (2013). "Role of the cytoskeleton and membrane trafficking in axon-dendrite morphogenesis," in *Cellular Migration and Formation of Neuronal Connections: Comprehensive Developmental Neuroscience,* eds J. L. Rubenstein and P. Rakic (San Diego,CA: Academic Press), 82–116.

Forman, M. S., Squier, W., Dobyns, W. B., and Golden, J. A. (2005). Genotypically defined lissencephalies show distinct pathologies. *J. Neuropathol. Exp. Neurol.* 64, 847–857. doi: 10.1097/01.jnen.0000182978.56612.41

Friocourt, G., Kappeler, C., Saillour, Y., Fauchereau, F., Rodriguez, M. S., Bahi, N., et al. (2005). Doublecortin interacts with the ubiquitin protease DFFRX, which associates with microtubules in neuronal processes. *Mol. Cell. Neurosci.* 28, 153–164. doi: 10.1016/j.mcn.2004.09.005

Fry, A. E., Cushion, T. D., and Pilz, D. T. (2014). The genetics of lissencephaly. *Am. J. Med. Genet. C Semin. Med. Genet.* 166C, 198–210. doi: 10.1002/ajmg.c.31402

Gleeson, J. G., Lin, P. T., Flanagan, L. A., and Walsh, C. A. (1999). Doublecortin is a microtubule-associated protein and is expressed widely by migrating neurons. *Neuron* 23, 257–271. doi: 10.1016/S0896-6273(00)80778-3

Gleeson, J. G., Minnerath, S., Kuzniecky, R. I., Dobyns, W. B., Young, I. D., Ross, M. E., et al. (2000). Somatic and germline mosaic mutations in the doublecortin gene are associated with variable phenotypes. *Am. J. Hum. Genet.* 67, 574–581. doi: 10.1086/303043

Guerrini, R. (2005). Genetic malformations of the cerebral cortex and epilepsy. *Epilepsia* 46(Suppl. 1), 32–37. doi: 10.1111/j.0013-9580.2005.461010.x

Guerrini, R., Moro, F., Kato, M., Barkovich, A. J., Shiihara, T., McShane, M. A., et al. (2007). Expansion of the first PolyA tract of *ARX* causes infantile spasms and status dystonicus. *Neurology* 69, 427–433. doi: 10.1212/01.wnl.0000266594.16202.c1

Hersheson, J., Mencacci, N. E., Davis, M., MacDonald, N., Trabzuni, D., Ryten, M., et al. (2013). Mutations in the autoregulatory domain of beta-tubulin 4a cause hereditary dystonia. *Ann. Neurol.* 73, 546–553. doi: 10.1002/ana.23832

Hong, S. E., Shugart, Y. Y., Huang, D. T., Shahwan, S. A., Grant, P. E., Hourihane, J. O., et al. (2000). Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with human *RELN* mutations. *Nat. Genet.* 26, 93–96. doi: 10.1038/79246

Jaglin, X. H., Poirier, K., Saillour, Y., Buhler, E., Tian, G., Bahi-Buisson, N., et al. (2009). Mutations in the beta-tubulin gene TUBB2B result in asymmetrical polymicrogyria. *Nat. Genet.* 41, 746–752. doi: 10.1038/ng.380

Jansen, A. C., Oostra, A., Desprechins, B., De Vlaeminck, Y., Verhelst, H., Regal, L., et al. (2011). *TUBA1A* mutations: from isolated lissencephaly to familial polymicrogyria. *Neurology* 76, 988–992. doi: 10.1212/WNL.0b013e31821043f5

Kato, M., Das, S., Petras, K., Kitamura, K., Morohashi, K., Abuelo, D. N., et al. (2004). Mutations of *ARX* are associated with striking pleiotropy and consistent genotype-phenotype correlation. *Hum. Mutat.* 23, 147–159. doi: 10.1002/humu.10310

Kato, M., and Dobyns, W. B. (2003). Lissencephaly and the molecular basis of neuronal migration. *Hum. Mol. Genet.* 12 Spec No 1, R89–R96. doi: 10.1093/hmg/ddg086

Kato, M., and Dobyns, W. B. (2005). X-linked lissencephaly with abnormal genitalia as a tangential migration disorder causing intractable epilepsy: proposal for a new term, "interneuronopathy." *J. Child Neurol.* 20, 392–397. doi: 10.1177/08830738050200042001

Kato, M., Kanai, M., Soma, O., Takusa, Y., Kimura, T., Numakura, C., et al. (2001). Mutation of the doublecortin gene in male patients with double cortex syndrome: somatic mosaicism detected by hair root analysis. *Ann. Neurol.* 50, 547–551. doi: 10.1002/ana.1231

Kato, M., Koyama, N., Ohta, M., Miura, K., and Hayasaka, K. (2010). Frameshift mutations of the *ARX* gene in familial Ohtahara syndrome. *Epilepsia* 51, 1679–1684. doi: 10.1111/j.1528-1167.2010.02559.x

Kato, M., Saitoh, S., Kamei, A., Shiraishi, H., Ueda, Y., Akasaka, M., et al. (2007). A longer polyalanine expansion mutation in the *ARX* gene causes early infantile epileptic encephalopathy with suppression-burst pattern (Ohtahara syndrome). *Am. J. Hum. Genet.* 81, 361–366. doi: 10.1086/518903

Keays, D. A., Tian, G., Poirier, K., Huang, G. J., Siebold, C., Cleak, J., et al. (2007). Mutations in alpha-tubulin cause abnormal neuronal migration in mice and lissencephaly in humans. *Cell* 128, 45–57. doi: 10.1016/j.cell.2006.12.017

Kitamura, K., Yanazawa, M., Sugiyama, N., Miura, H., Iizuka-Kogo, A., Kusaka, M., et al. (2002). Mutation of *ARX* causes abnormal development of forebrain and testes in mice and X-linked lissencephaly with abnormal genitalia in humans. *Nat. Genet.* 32, 359–369. doi: 10.1038/ng1009

Kumar, R. A., Pilz, D. T., Babatz, T. D., Cushion, T. D., Harvey, K., Topf, M., et al. (2010). *TUBA1A* mutations cause wide spectrum lissencephaly (smooth brain) and suggest that multiple neuronal migration pathways converge on alpha tubulins. *Hum. Mol. Genet.* 19, 2817–2827. doi: 10.1093/hmg/ddq182

Marsh, E., Fulp, C., Gomez, E., Nasrallah, I., Minarcik, J., Sudi, J., et al. (2009). Targeted loss of Arx results in a developmental epilepsy mouse model and recapitulates the human phenotype in heterozygous females. *Brain* 132, 1563–1576. doi: 10.1093/brain/awp107

Moheb, L. A., Tzschach, A., Garshasbi, M., Kahrizi, K., Darvish, H., Heshmati, Y., et al. (2008). Identification of a nonsense mutation in the very low-density lipoprotein receptor gene (VLDLR) in an Iranian family with dysequilibrium syndrome. *Eur. J. Hum. Genet.* 16, 270–273. doi: 10.1038/sj.ejhg.5201967

Poirier, K., Keays, D. A., Francis, F., Saillour, Y., Bahi, N., Manouvrier, S., et al. (2007). Large spectrum of lissencephaly and pachygyria phenotypes resulting from de novo missense mutations in tubulin alpha 1A (*TUBA1A*). *Hum. Mutat.* 28, 1055–1064. doi: 10.1002/humu.20572

Poirier, K., Lebrun, N., Broix, L., Tian, G., Saillour, Y., Boscheron, C., et al. (2013). Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly. *Nat. Genet.* 45, 639–647. doi: 10.1038/ng.2613

Poirier, K., Saillour, Y., Bahi-Buisson, N., Jaglin, X. H., Fallet-Bianco, C., Nabbout, R., et al. (2010). Mutations in the neuronal ss-tubulin subunit TUBB3 result in malformation of cortical development and neuronal migration defects. *Hum. Mol. Genet.* 19, 4462–4473. doi: 10.1093/hmg/ddq377

Poolos, N. P., Das, S., Clark, G. D., Lardizabal, D., Noebels, J. L., Wyllie, E., et al. (2002). Males with epilepsy, complete subcortical band heterotopia, and somatic mosaicism for DCX. *Neurology* 58, 1559–1562. doi: 10.1212/WNL.58.10.1559

Romaniello, R., Arrigoni, F., Cavallini, A., Tenderini, E., Baschirotto, C., Triulzi, F., et al. (2014). Brain malformations and mutations in alpha- and beta-tubulin genes: a review of the literature and description of two new cases. *Dev. Med. Child Neurol.* 56, 354–360. doi: 10.1111/dmcn.12370

Ross, M. E., Swanson, K., and Dobyns, W. B. (2001). Lissencephaly with cerebellar hypoplasia (LCH): a heterogeneous group of cortical malformations. *Neuropediatrics* 32, 256–263. doi: 10.1055/s-2001-19120

Simons, C., Wolf, N. I., McNeil, N., Caldovic, L., Devaney, J. M., Takanohashi, A., et al. (2013). A *de novo* mutation in the beta-tubulin gene TUBB4A results in the leukoencephalopathy hypomyelination with atrophy of the basal ganglia and cerebellum. *Am. J. Hum. Genet.* 92, 767–773. doi: 10.1016/j.ajhg.2013.03.018

Smith, D. S., Niethammer, M., Ayala, R., Zhou, Y., Gambello, M. J., Wynshaw-Boris, A., et al. (2000). Regulation of cytoplasmic dynein behaviour and microtubule organization by mammalian Lis1. *Nat. Cell Biol.* 2, 767–775. doi: 10.1038/35041000

Stevens, E., Carss, K. J., Cirak, S., Foley, A. R., Torelli, S., Willer, T., et al. (2013). Mutations in B3GALNT2 cause congenital muscular dystrophy and hypoglycosylation of alpha-dystroglycan. *Am. J. Hum. Genet.* 92, 354–365. doi: 10.1016/j.ajhg.2013.01.016

Stromme, P., Mangelsdorf, M. E., Shaw, M. A., Lower, K. M., Lewis, S. M., Bruyere, H., et al. (2002). Mutations in the human ortholog of *Aristaless* cause X-linked mental retardation and epilepsy. *Nat. Genet.* 30, 441–445. doi: 10.1038/ng862

Tischfield, M. A., Baris, H. N., Wu, C., Rudolph, G., Van Maldergem, L., He, W., et al. (2010). Human TUBB3 mutations perturb microtubule dynamics, kinesin interactions, and axon guidance. *Cell* 140, 74–87. doi: 10.1016/j.cell.2009.12.011

Viot, G., Sonigo, P., Simon, I., Simon-Bouy, B., Chadeyron, F., Beldjord, C., et al. (2004). Neocortical neuronal arrangement in LIS1 and DCX lissencephaly may be different. *Am. J. Med. Genet. A* 126, 123–128. doi: 10.1002/ajmg.a.20569

Vuillaumier-Barrot, S., Bouchet-Seraphin, C., Chelbi, M., Devisme, L., Quentin, S., Gazal, S., et al. (2012). Identification of mutations in TMEM5 and ISPD as a cause of severe cobblestone lissencephaly. *Am. J. Hum. Genet.* 91, 1135–1143. doi: 10.1016/j.ajhg.2012.10.009

Yoneda, Y., Haginoya, K., Kato, M., Osaka, H., Yokochi, K., Arai, H., et al. (2013). Phenotypic spectrum of *COL4A1* mutations: porencephaly to schizencephaly. *Ann. Neurol.* 73, 48–57. doi: 10.1002/ana.23736

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Jpn J Ophthalmol
DOI 10.1007/s10384-015-0370-8

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

CLINICAL INVESTIGATION

Clinical characteristics of congenital and developmental cataract undergoing surgical treatment

Toshiyuki Nagamoto · Tetsuro Oshika · Takashi Fujikado · Tatsuro Ishibashi · Miho Sato · Mineo Kondo · Daijiro Kurosaka · Noriyuki Azuma

Received: 24 September 2014 / Accepted: 19 December 2014

Abstract
Purpose To analyze the clinical characteristics of congenital/developmental cataract undergoing surgery.
Methods A mail questionnaire was sent to 49 facilities engaged in surgical treatment of congenital cataracts, and data on preoperative clinical features were collected.
Results Twenty nine facilities reported on 864 eyes of 521 patients with congenital/infantile cataract, ranging in age at initial visit from 0 to 18.8 years (2.6 ± 3.3 years, mean ± standard deviation). Among the patients, 65.8 % had bilateral cataracts and 34.2 % were unilaterally affected. Family history was found for 22.4 % of cases, of which 98.1 % were bilateral. Family history was positive for 33.1 % of bilateral and 1.3 % of unilateral cases. The most common main complaint was white pupil for 35.7 % of bilateral cases and 32.7 % for unilateral cases. Concomitant systemic abnormalities were more frequently associated with bilateral cases (31.6 %) than with unilateral cases (16.7 %). Associated ocular diseases, such as strabismus, persistent fetal vasculature, and posterior lenticonus, were more frequently seen among unilateral cases whereas nystagmus was more common among bilateral cases.
Conclusions Among congenital/developmental cataracts, the ratio of bilateral and unilateral cases was approximately 2:1. Almost all patients with a family history of congenital cataract were bilateral. Initial visits to a physician were rather late, 2.6 years from birth; this should be improved.

Keywords Congenital cataract · Developmental cataract · White pupil · Family history · Cataract surgery

T. Nagamoto
Department of Ophthalmology, Kyorin University School of Medicine, Tokyo, Japan

T. Nagamoto
Nagamoto Eye Clinic, Tokyo, Japan

T. Oshika (✉)
Department of Ophthalmology, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan
e-mail: oshika@eye.ac

T. Fujikado
Department of Applied Visual Science, Osaka University Graduate School of Medicine, Osaka, Japan

T. Ishibashi
Department of Ophthalmology, Kyusyu University, Graduate School of Medicine, Fukuoka, Japan

M. Sato
Department of Ophthalmology, Hamamatsu University School of Medicine, Shizuoka, Japan

M. Kondo
Department of Ophthalmology, Mie University Graduate School of Medicine, Mie, Japan

D. Kurosaka
Department of Ophthalmology, Iwate Medical University, Iwate, Japan

N. Azuma
Department of Ophthalmology and Cell Biology, National Center for Child Health and Development, Tokyo, Japan

Published online: 23 January 2015

Introduction

Although surgical treatment of cataracts in childhood has continued to evolve in economically developed nations [1], overall surgical and visual outcomes for pediatric cataract patients is suboptimum compared with those for adult cataract patients. Because childhood cataracts are a major cause of avoidable blindness [2, 3], early detection and timely treatment of congenital/developmental cataracts are crucial to preventing irreversible visual impairment among children. It is clinically important to analyze the preoperative features of congenital/developmental cataract in detail for planning of comprehensive strategies in tackling childhood cataracts. However, there are few studies of the clinical characteristics of cases with congenital/developmental cataract undergoing surgery [4–7], especially in Asian countries. We conducted a retrospective, mail questionnaire study to investigate the clinical features of congenital/developmental cataracts in Japan.

Patients and methods

A mail survey was sent to 49 facilities known to be conducting surgical treatment of congenital/developmental cataracts in Japan, to enquire about cases operated on between January 2005 and December 2009. Twenty-nine facilities reported on 872 eyes of 526 patients. Among these, patients 20 years of age and older, patients with congenital ectopia lentis, and cases of secondary implantation of an intraocular lens (IOL) were excluded, and data for the remaining 864 eyes of 521 patients were used for the subsequent analysis. Because the exact distinction between congenital and developmental cataract is difficult, both of these clinical entities were included in this study. The study received approval from the institutional review committee of Kyorin University School of Medicine.

Results

Laterality

Among the patients, 65.8 % (343) had bilateral cataracts and 34.2 % (178) were unilaterally affected, so the ratio of bilateral to unilateral cases was approximately 2:1.

Family history of congenital cataracts

Forty-eight cases for which information was not available were excluded, and the remaining 473 patients were analyzed. Family history was found for 22.4 % (106 cases), of which 98.1 % were bilateral cases. Family history was positive for 33.1 % of bilateral cases and 1.3 % of unilateral cases, which were significantly different from each other (χ^2 test, $p < 0.0001$). The mode of inheritance was not investigated in this study.

Associated systemic diseases

Seventy-seven cases were excluded from the analysis because of lack of clear information about systemic comorbidities. For the remaining 444 patients, 118 cases (26.6 %) had some form of systemic disorder. Prevalence was significantly higher among bilateral cases (93/294, 31.6 %) than among unilateral cases (25/150, 16.7 %) ($p = 0.0007$). When the incidence of individual diseases was studied, mental retardation was significantly more frequent among bilateral than among unilateral cases ($p = 0.004$); other systemic abnormalities were not statistically different between these groups (Table 1).

Associated ocular diseases

Data were not available for several cases. As shown in Table 2, nystagmus was more frequently seen among bilateral than among unilateral cases ($p < 0.0001$) whereas strabismus ($p < 0.0001$), persistent fetal vasculature ($p < 0.0001$), and posterior lenticonus ($p = 0.046$) were significantly more common among unilateral cases.

Main complaints

The most common complaint at the initial visit was white pupil for 34.7 % followed by, in a descending order, poor vision for 23.5 %, strabismus for 12.0 %, cataract diagnosed by a previous physician for 9.1 %, cataract found with other diseases for 5.9 %, nystagmus for 5.7 %, photophobia for 4.3 %, family history for 3.0 %, and poor visual fixation for 1.8 %.

When bilateral and unilateral cases were compared (Table 3), bilateral cases had significantly greater incidence of nystagmus ($p < 0.05$) and family history ($p < 0.05$) whereas unilateral cases were significantly more frequently associated with strabismus ($p < 0.05$).

Age at initial visit

When the patients were first seen by ophthalmologists at the facilities participating in this study, their average age was 2.6 ± 3.3 years (mean ± standard deviation; range 0 to 18.8 years). The median was 1.2 years and the interquartile range was from 3 months to 3.8 years.

It is reported that to achieve a good visual outcome for congenital unilateral cataracts surgery should be performed before 6 weeks after birth, to minimize the effect of visual

Table 1 Associated systemic disorders

	Bilateral cases ($n = 294$)	Unilateral cases ($n = 150$)	p value*
Chromosomal disorder			
Down syndrome	24 (8.2 %)	5 (3.3 %)	n.s.
Others	4 (1.4 %)	3 (2.0 %)	n.s.
Intrauterine infection			
Rubella	2 (0.7 %)	1 (0.7 %)	n.s.
TORCH syndrome	1 (0.3 %)	0	n.s.
Central nervous system abnormality			
Mental retardation	20 (6.8 %)	1 (0.7 %)	$p < 0.05$
Epilepsy	6 (2.0 %)	1 (0.7 %)	n.s.
Others	9 (3.1 %)	1 (0.7 %)	n.s.
Cardiac anomaly	21 (7.1 %)	1 (0.7 %)	n.s.
Low birth weight	9 (3.1 %)	3 (2.0 %)	n.s.
Others	21 (7.1 %)	10 (6.7 %)	n.s.

* Bilateral and unilateral cases were compared by use of the χ^2 test

n.s. not significant

Table 2 Associated ocular disorders

	Bilateral cases	Unilateral cases	p value*
Strabismus (cases)	78/309 (25.4 %)	79/163 (48.5 %)	$p < 0.0001$
Nystagmus (cases)	75/307 (24.4 %)	6/150 (4.0 %)	$p < 0.0001$
Microcornea (eyes)	45/686 (6.6 %)	7/177 (4.0)	n.s.
Nanophthalmos (eyes)	25/686 (3.6 %)	6/177 (3.4 %)	n.s.
Persistent fetal vasculature (eyes)	3/686 (0.4 %)	14/177 (7.9 %)	$p < 0.0001$
Posterior lenticonus (eyes)	7/686 (1.0 %)	6/177 (3.4 %)	$p < 0.05$
Others (eyes)	38/686 (5.5 %)	12/177 (6.8 %)	n.s.

* Bilateral and unilateral cases were compared by use of the χ^2 test

n.s. not significant

Table 3 Main complaints at initial visit

Main complaint	Bilateral cases	Unilateral cases	p values*
White pupil	117/328 (35.7 %)	54/165 (32.7 %)	n.s.
Poor vision	70/328 (21.3 %)	46/165 (27.9 %)	n.s.
Cataract diagnosed by previous physician	31/328 (9.5 %)	14/165 (8.5 %)	n.s.
Nystagmus	28/328 (8.5 %)	0	$p < 0.05$
Strabismus	25/328 (7.6 %)	34/165 (20.6 %)	$p < 0.05$
Other diseases	22/328 (6.7 %)	7/165 (4.2 %)	n.s.
Photophobia	15/328 (4.6 %)	6/165 (3.6 %)	n.s.
Family history	14/328 (4.3 %)	1/165 (0.6 %)	$p < 0.05$
Poor visual fixation	6/328 (1.8 %)	3/165 (1.8 %)	n.s.
Unknown	15/343	13/178	

* Bilateral and unilateral cases were compared by use of the χ^2 test

n.s. not significant

deprivation [8]. Likewise, for bilateral cases, the critical period for surgical treatment to achieve optimum orthoptics is reported to be 8 [9], 10 [10], or 14 weeks [11] of age. We defined the critical visual period to be 6 weeks for unilateral cases and 12 weeks for bilateral cases and, following these guidelines, analyzed the patients in our survey. It was found that 15.2 % (25/165 cases) of unilateral cases first visited the physician within 6 weeks and 31.4 % (103/328 cases) of bilateral cases were seen for the first time within 12 weeks after birth.

Main complaints and age at initial visit

The relationship between main complaint and age at the initial visit was analyzed. For unilateral cases, 42.6 % of cases with white pupil and 28.6 % with cataract found with other diseases visited the physician within 6 weeks of birth. No cases with other main complaints were seen within the critical period. Among bilateral cases, the percentage of patients who underwent ocular examination within 12 weeks of birth was 64.3 % with family history of

congenital cataract, 51.3 % with white pupil, 40.9 % with cataract found with other diseases, 33.3 % with poor visual fixation, 32.3 % with cataract diagnosed by previous physicians, 28.6 % with nystagmus, 13.3 % with photophobia, 8.0 % with strabismus, and 1.4 % with poor vision.

The timing of first visit to ophthalmologists was earliest for those with nystagmus (5.4 ± 4.3 months) followed by, in descending order, poor visual fixation (9.0 ± 8.7 months), white pupil (9.7 ± 21.2 months), family history (10.8 ± 21.7 months), cataract diagnosed with other diseases (11.1 ± 19.9 months), photophobia (29.2 ± 14.5 months), strabismus (38.2 ± 34.3 months), cataract diagnosed by previous physicians (47.4 ± 69.4 months), and poor vision (81.3 ± 46.8 months).

Family history and other variables

Because more than 98 % of unilateral cases had no family history, the relationship between family history and other variables were analyzed for bilateral cases.

The average age at initial visit for cases with family history was 2.5 ± 3.4 years whereas that for cases without family history was 2.5 ± 3.6 years (no significant difference; Student t test, $p = 0.851$). The incidence of associated ocular anomalies did not differ between the two groups (15.4 vs. 15.7 %). The prevalence of associated systemic problems was significantly lower among cases with family history (5.8 %) than among those without (35.7 %) ($p < 0.0001$).

Cataract morphology

Because cataract morphology for both eyes was similar for more than 90 % of bilateral cases, analysis was based on the number of cases rather than the number of eyes, after exclusion of those for which valid information was not available.

The common morphological type of cataract included total cataract (29.3 %), nuclear cataract (19.4 %), and lamellar cataract (18.5 %) in bilateral cases whereas posterior subcapsular/polar cataract (34.7 %), nuclear cataract (23.5 %), and total cataract (21.8 %) were frequently found in unilateral cases. These numbers were calculated including those with unknown and other type of cataract, and thus are different from those shown in Table 4.

Bilateral and unilateral cases were compared after excluding cases with unknown type, bilaterally different type, and other type of cataract (Table 4). The percentage of total ($p < 0.05$) and lamellar cataracts ($p < 0.05$) was significantly greater among bilateral cases whereas posterior subcapsular/polar cataracts were more frequent in unilateral cases ($p < 0.05$).

Cataract morphology and other variables

Age at initial visit is plotted as a function of cataract morphology in Fig. 1. Cases with anterior subcapsular/polar cataract visited the physician earliest, followed by those with total, nuclear, combined, lamellar and posterior subcapsular/polar cataracts. Statistical analysis revealed that age at initial visit was significantly lower for patients with anterior subcapsular, total, and nuclear cataract than for those with lamellar and posterior subcapsular cataract ($p < 0.05$, Kruskal–Wallis test, Scheffe multiple comparison).

For cases with total cataract, age at the initial visit was significantly lower for bilateral (12.3 ± 21.3 months) than unilateral cases (25.7 ± 34.4 months) ($p = 0.0314$, Welch t-test). Such differences were not found for cases with other cataract morphology.

The relationship between cataract morphology and family history was analyzed for bilateral cases. Family history was found in 30.6 % of cases with total opacity, 27.1 % of cases with lamellar opacity, 44.8 % of cases with nuclear opacity, 41.2 % of cases with posterior subcapsular/polar opacity, 33.3 % of cases with anterior subcapsular/polar opacity, 43.8 % of cases with combined opacity, 21.2 % of cases with a different type of opacity bilaterally, and 28.6 % of cases with another type of opacity. These percentages were not statistically significantly different.

Table 4 Cataract morphology

Percentages are calculated after excluding cases with bilaterally different type, other type, and unknown type of cataract, to compare bilateral and unilateral cases

n.s. not significant

* Bilateral and unilateral cases were compared by use of the χ^2 test

Morphology	Bilateral cases	Unilateral cases	p value*
Total	95/281 (33.8 %)	37/169 (21.9 %)	$p < 0.05$
Lamellar	60/281 (21.4 %)	11/169 (6.5 %)	$p < 0.05$
Nuclear	63/281 (22.4 %)	40/169 (23.7 %)	n.s.
Posterior capsular/polar	23/281 (8.2 %)	59/169 (34.9 %)	$p < 0.05$
Anterior capsular/polar	6/281 (2.1 %)	5/169 (3.0 %)	n.s.
Combined	34/281 (12.1 %)	17/169 (10.1 %)	n.s.
Different bilaterally	37/343	–	–
Others	6/343	1/178	–
Unknown	19/343	8/178	–

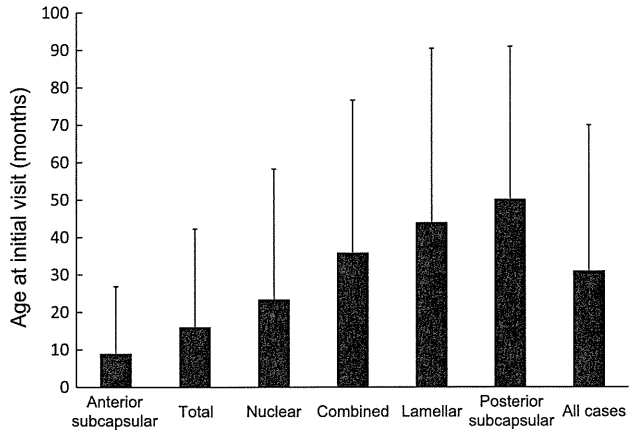

Fig. 1 Age at initial visit (months) as a function of cataract morphology

There was no significant association between cataract morphology and prevalence of associated systemic disorders. For cases with total cataract, the incidence of systemic disorders was 37.6 % among bilateral cases and 15.6 % among unilateral cases, which was significantly different ($p = 0.022$). For cases with nuclear cataracts, the incidence of systemic abnormalities was significantly higher for bilateral cases (32.8 %) than for unilateral cases (2.9 %) ($p = 0.0007$). Such differences were not found for cases of cataracts with a different morphology.

The relationship between cataract morphology and incidence of associated ocular comorbidities was assessed (Table 5). It was found that cases with total cataracts were frequently associated with strabismus, nystagmus, and microphthalmos whereas nuclear cataract cases presented high prevalence of microcornea. Persistent fetal vasculature and posterior lenticonus were more often seen for eyes with posterior subcapsular/polar cataract than for those with other cataract morphology.

Presumed etiology of congenital cataract

The etiology was estimated from the data provided by the survey and classified into several categories, including hereditary, congenital ocular abnormality, congenital systemic diseases, and unknown (Table 6). Whenever family history of congenital/developmental cataract was positive, it was judged to be hereditary.

Among 343 bilateral cases, unknown etiology (idiopathic) was most common among 123 cases (35.9 %), followed by hereditary (104 cases, 30.3 %), systemic anomalies (80 cases, 23.3 %), and congenital ocular abnormality (26 cases, 10.5 %).

Among 178 unilateral cases, the presumed etiology was unknown for 121 (68.0 %), congenital ocular abnormality for 38 cases (21.3 %), systemic diseases for 17 cases (9.6 %), and hereditary for 2 cases (1.1 %).

Table 6 Presumed etiology of congenital cataract

Etiology	Bilateral cases	Unilateral cases
Hereditary (family history)	104 (30.3 %)	2 (1.1 %)
Congenital ocular abnormality	36 (10.5 %)	38 (21.3 %)
Persistent fatal vasculature	3	14
Nanophthalmos	11	6
Microcornea	12	5
Others	10	13
Systemic diseases	80 (23.3 %)	17 (9.6 %)
Chromosomal disorder		
Down syndrome	24	4
Others	4	3
Intrauterine infection		
Rubella	2	1
TORCH	1	0
Central nervous system abnormality		
Mental retardation	6	0
Epilepsy	6	0
Others	13	0
Cardiac anomaly	10	1
Low birth weight	6	3
Other systemic diseases	8	5
Unknown	123 (35.9 %)	121 (68.0 %)
Total	343	178

Table 5 Frequently associated ocular comorbidities and cataract morphology

Ocular diseases	Bilateral cases	Unilateral cases
Strabismus	Total, different bilaterally	Nuclear
Nystagmus	Total	–
Microcornea	Nuclear	–
Microphthalmos	Anterior subcapsular/polar, total	Total
Persistent fetal vasculature	Posterior subcapsular/polar	Posterior subcapsular/polar
Posterior lenticonus	Posterior subcapsular/polar	–

Discussion

This study population was confined to those undergoing surgical treatment for congenital/developmental cataracts; patients whose surgical intervention was not indicated were not included. This was because, when planning this retrospective study, we believed that more detailed clinical data would be available for surgical cases than for non-surgical cases. Thus, it should be noted that these results do not necessarily give a complete picture of cases with congenital/developmental cataract in general. Cases with unilateral dense cataracts diagnosed too late for surgery and those with severe preexisting ocular anomalies contraindicated to cataract surgery were not included in this study. Likewise patients with severe systemic comorbidities at a high risk of developing complications in general anesthesia were excluded from the current study population. Nevertheless, another study among facilities similar to those in this study showed that more than 85 % of respondents will recommend surgery for congenital cataract even when visual prognosis may not be very promising, after fully explaining the pros and cons of surgery to the patients' family. Therefore, we believe that the results obtained herein do not deviate substantially from the overall situation for congenital/developmental cataracts in Japan.

Laterality

In 2000, Rahi et al. [12] studied 243 cases with congenital cataracts in the UK and reported that 66 % were bilateral. A Danish study by Haargaard et al. [13] in 2004 reported that 64 % of 1,027 congenital cataracts were bilateral, and an Australian study by Wirth et al. in 2002 found that 56 % of 421 cases had cataracts in both eyes [14]. These studies were conducted nationwide and/or across wider regions, and their results are in good agreement with ours. Smaller-scale studies, however, report different results. Eckstein et al. [15] investigated 366 cases in India and reported an incidence of bilateral cases of 78.1 %, of which 15 % were caused by rubella; Jain et al. [16] reported that 92.1 % of 76 congenital cataracts were bilateral. SanGiovanni et al. [17] stated that 47.9 % of 73 congenital cataracts in the USA were bilateral. Judging from previous large-scale studies and our current results, it seems that the ratio of bilateral and unilateral cases in congenital cataract is approximately 2:1.

Family history of congenital cataract

We found that family history was significantly higher for bilateral cases (33.1 %) than for unilateral cases (1.3 %), in good agreement with results reported by Rahi et al. [12] and Haargaard et al. [13].

Associated systemic diseases

Consistent with our results, Rahi et al. [12] and Haargaard et al. [13] reported that the incidence of associated systemic comorbidities was higher for bilateral cases than for unilateral cases.

Associated systemic anomalies were found for 35.7 % of patients without a family history of congenital cataract, compared with only 5.8 % of those with family history. The prevalence of preexisting ocular problems was not associated with family history of congenital cataract, however. These results suggest that many patients with hereditary congenital cataract have no concurrent systemic and ocular diseases other than cataract. Haargaard et al. [13] also reported that 91 % of cases with hereditary congenital cataract had no abnormality other than cataract (isolated cataract).

Associated ocular diseases

We found that strabismus accompanied congenital/developmental cataracts among 33.3 % of patients, which is consistent with results from previous studies, for example 24.1 % reported by Deweese [18], 33.6 % reported by Yang et al. [19], and 28 % reported by Kim et al. [20].

The incidence of nystagmus associated with congenital cataract varies: 22.6 % reported by Deweese [18], 38.1 % reported by Yang et al. [19], and 15 % reported by Kim et al. [20]. Our results (17.7 %) fall within this range.

The prevalence of microphthalmos associated with congenital cataract was reported to be 4.5 % by Deweese [18] and 6.6 % by Rahi et al. [12]. The prevalence of either microphthalmos or microcornea was reported to be 3.9 % by Haargaard et al. [13], and the prevalence of microcornea was 10.8 % among cases in the study by Yang et al. [19]. In many of these studies, microphthalmos and microcornea are not distinguished clearly. In this study, we found microphthalmos in 3.6 % and microcornea in 6.0 % of cases. When combined, either microphthalmos or microcornea was present in 8.6 % (45/521).

Persistent fetal vasculature often coexists with congenital cataract, and its incidence is reported to be 3.8 % by Yang et al. [19], 5.7 % by Haargaard et al. [13], 8.2 % by Rahi et al. [12], 4.3 % by Ledoux et al. [21], and 3.0 % by Plager et al. [22] The prevalence found in our study, 2.0 %, is somehow lower than in these reports.

The incidence of posterior lenticonus in eyes with congenital cataracts varies substantially, depending on the study: 0.9 % reported by Haargaard et al. [13], 10.1 % by Ledoux et al. [21], and 14.9 % by Plager et al. [22]. In our study, 1.5 % of cases presented with posterior lenticonus. These discrepancies may be because of different study populations, different surgical procedures, and/or timing of

diagnosis. Diagnosis of posterior lenticonus is sometimes difficult before surgery, because of dense opacity, and even during surgery, when the lens is being removed by use of the pars plana lensectomy technique. In fact, one of the authors (TN) found posterior lenticonus in 9.8 % (6/61) of cases during surgery in which limbal approach technique with implantation of an intraocular lens was scheduled.

Concomitant ocular abnormalities, for example strabismus, persistent fatal vasculature, and posterior lenticonus, are more frequently associated with unilateral rather than bilateral cases of congenital cataract. For persistent fatal vasculature, Haargaard et al. [13] reported prevalence of 15.0 vs. 0.5 % (unilateral vs. bilateral, $p < 0.0001$) and Rahi et al. [12] reported 21.7 vs. 1.3 % ($p < 0.0001$). The incidence of posterior lenticonusis was reported to be 1.9 vs. 0.3 % ($p = 0.025$) by Haargaard et al. [13]. For the association of microphthalmos with congenital cataract, Rahi et al. [12] reported no difference between unilateral and bilateral cases (7.2 vs. 6.3 %, $p = 0.770$) whereas Haargaard et al. [13] reported that the prevalence of either microphthalmos or microcornea among patients with congenital cataracts was significantly larger for unilateral (5.9 %) than for bilateral (2.8 %) cases ($p = 0.0127$). We found the incidence of microphthalmos and microcornea to be no different between bilateral and unilateral cases.

Age at initial visit

In this study, age at the first visit to ophthalmologists averaged 2.6 ± 3.3 years (mean ± standard deviation; range 0 to 18.8 years). Yang et al. [19] reported an average age of 2 years 1 month (0–10 years 1 month) and Haargaard et al. [13] reported a medium age of 3 years; both results are very similar to ours. Patients in the UK were, however, examined and diagnosed at a very early stage, average 8 weeks (0–15 years) after birth, as reported by Rahi et al. [12]. This is because of the national ophthalmic surveillance scheme in the UK, administered ophthalmologists and pediatricians, in which all British pediatricians are required to conduct ocular examinations of newborns; screening by pediatricians and treatment by ophthalmologists are free of charge; and 89 % of ophthalmologists participate in the national survey of congenital/infantile cataracts and report to the registry [12].

There is a specific critical period for surgical treatment of congenital cataract to achieve optimum orthoptics. For unilateral cases, the report of 6 weeks from birth by Birch et al. [8] is widely accepted. For bilateral cases, there are several opinions, ranging from 8 [9] and 10 [10] to 14 weeks [11] from birth; we adopted 12 weeks as the threshold for this analysis. We found that only 15.2 % (25/165 cases) of unilateral cases and 31.4 % (103/328 cases) of bilateral cases were seen for the first time within the critical visual period, indicating that detection and diagnosis of congenital cataracts were too late in many cases.

The relationship between main complaint and age at the initial visit was analyzed. For bilateral cases, 64.3 % with a family history of congenital cataracts visited within 12 weeks, followed by 51.3 % with white pupil, and 40.9 % with cataract diagnosed with other eye diseases. For unilateral cases, the percentage of patients who saw a physician within the critical period was 42.6 % for those with white pupil and 28.6 % for those with cataract diagnosed with other eye diseases, compare with 0 % for other main complaints. Thus, two-thirds of the patients with family history visited within the critical period, and fewer than half of those with white pupil came to see a doctor within that period.

When studying the relationship between cataract morphology and age at initial visit, it was found that patients with total, anterior subcapsular, and nuclear opacity visited a physician significantly earlier than those with posterior subcapsular and lamellar opacity. This seems to be because total, anterior subcapsular, and nuclear cataract are often apparent from white pupils at an earlier stage, in contrast with posterior subcapsular and lamellar cataract.

Main complaints

Few studies have investigated the main complaints of patients with congenital/developmental cataract. Yang et al. [19] reported the distribution of initial presentations of suspected cataract: poor visual acuity or complaint of blurred vision for 33.3 %, white pupil for 31.5 %, discovery on screen test by pediatricians or at school for 19.8 %, squint for 10.8 %, eye shaking for 2 %, head tilt for 1.5 %, and photophobia for 1 %. The percentages of white pupil and squint in their report are similar to our results, but those of nystagmus and photophobia are inconsistently lower; the reason for this is currently unknown.

Cataract morphology

There are a variety of reports on the distribution of morphological types of cataract. Haargaard et al. [13] found nuclear or lamellar cataract among 34 %, total cataract among 15 %, posterior subcapsular cataract among 14 %, combined cataract among 10 %, posterior polar cataract among 10 %, anterior polar cataract among 6 %, others among 8 %, and unknown among 3 %. Compared with their results, we found a somewhat higher proportion of total cataracts and a lower proportion of posterior subcapsular/polar and anterior subcapsular/polar cataracts.

Yang et al. [19] reported a very high frequency of nuclear cataracts (48.4 %) compared with total (22.4 %),

posterior polar (13.8 %), and lamellar (8.5 %) cataracts. Plager et al. [22] found lamellar among 35.8 % of cases, nuclear among 16.4 %, posterior subcapsular/polar among 38.8 %, total among 6.0 %, and anterior polar cataract among 1.5 %. Ledoux et al. [21] state that lamellar opacity was present among 30.9 %, nuclear among 24.5 %, posterior subcapsular among 14.4 %, posterior lenticonus among 10.1 %, posterior polar among 7.9 %, total among 2.9 %, anterior polar opacity among 2.9 %, and others among 2.2 %. These conflicting results seem suggestive of different surgical indications for congenital cataracts, and diverse background of patients, for example age, ethnicity, and socioeconomic situations.

The distribution of cataract morphology did not differ substantially between those with and without family history of congenital cataracts, indicating that inherited and non-inherited congenital cataracts are no different in their phenotype. Haargaard et al. [13]. stated that hereditary cataracts tend to be more associated with nuclear and lamellar cataracts, whereas idiopathic types are more likely to be linked with posterior subcapsular/polar cataracts, but they did not show a statistically significant difference between them.

There is no study of the relationship between cataract morphology and the incidence of ocular comorbidities. We found that cases with total cataract were frequently associated with strabismus, nystagmus, and microphthalmos whereas persistent fetal vasculature and posterior lenticonus were more often seen for eyes with posterior subcapsular/polar cataracts than for those with other cataract morphology. These results can be explained by the fact that total cataract results in more severe visual deprivation, leading to strabismus and nystagmus at an early stage, whereas posterior fetal vasculature and posterior lenticonus are anatomically related to posterior subcapsular/polar cataracts.

Presumed etiology of congenital cataract

The distribution of presumed etiology in this study is in good agreement with that reported by Rahi et al. [13], who reported that 34 % of bilateral cases were of unknown etiology, 28 % were hereditary, 25 % were associated with systemic diseases, and 13 % were linked to ocular diseases. They also reported a higher proportion of unilateral cases associated with ocular comorbidities, however [12]. This is because their statistics include unilateral cases with persistent hyperplastic primary vitreous and anterior segment dysgeneses, severe cases of which were excluded from our study population because of the absence of surgical indications. The breakdown of presumed etiology reported by Haargaard et al. [13] is highly consistent with our results for both bilateral and unilateral cases.

In conclusion, we herein report the clinical features of cases with congenital/infantile cataracts who underwent surgical treatment. Understanding the detailed clinical characteristics of these cases and analyzing the relationships among the different variables will be of clinical importance to achieving earlier diagnosis and providing timely treatment of congenital/developmental cataract to prevent potentially treatable amblyopia in children.

Acknowledgments Supported by the Health and Labour Sciences Research Grant, Research on Measures for Intractable Diseases, The Ministry of Health Labour and Welfare, Japan. We thank all physicians who contributed to this study by providing valuable information, those from National Center for Child Health and Development, Hyogo Prefectural Kobe Children's Hospital, Aichi Children's Health and Medical Center, Osaka City General Hospital, Kyorin University School of Medicine, Fukushima Medical University, Osaka Medical Center and Research Institute for Maternal and Child Health, Iwate Medical University, University of Tsukuba Faculty of Medicine, Dokkyo Medical University, Kagoshima University Faculty of Medicine, Kanagawa Children's Medical Center, Hamamatsu University School of Medicine, Osaka University Medical School, Keio University School of Medicine, Kurume University School of Medicine, Wakayama Medical University, Kagawa University Faculty of Medicine, Kanazawa University School of Medicine, University of Fukui Faculty of Medical Science, Shiga University of Medical Science, Ehime University School of Medicine, Toho University Omori Medical Center, Shinshu University School of Medicine, Kyushu University School of Medicine, Kobe University School of Medicine, Nagoya University School of Medicine, Hokkaido Children's Hospital and Medical Center, and Kagawa National Children's Hospital.

Conflicts of interest T. Nagamoto, None; T. Oshika, None; T. Fujikado, None; T. Ishibashi, None; M. Sato, None; M. Kondo, None; D. Kurosaka, None; N. Azuma, None.

References

1. Taylor D. Congenital cataract: the history, the nature and the practice: the Doyne Lecture. Eye. 1998;12:9–36.
2. Gilbert C, Foster A. Childhood blindness in the context of VISION 2020–the right to sight. Bull World Health Organ. 2001;79:227–32.
3. Thylefors B. A global initiative for the elimination of avoidable blindness. Commun Eye Health. 1998;11:1–3.
4. Zetterström C, Lundvall A, Kugelberg M. Cataracts in children. J Cataract Refract Surg. 2005;31:824–40.
5. Lambert SR, Drack AV. Infantile cataracts. Surv Ophthalmol. 1996;40:427–58.
6. Hiles DA, Carter BT. Classification of cataracts in children. Int Ophthalmol Clin. 1977;17:15–29.
7. Hiles DA. Infantile cataracts. Pediatr Ann. 1983;12:556–73.
8. Birch EE, Stager DR. The critical period for surgical treatment of dense congenital unilateral cataract. Invest Ophthalmol Vis Sci. 1996;37:1532–8.
9. Gelbart SS, Hoyt CS, Jastrebski G, Marg E. Long-term visual results in bilateral congenital cataracts. Am J Ophthalmol. 1982;93:615–21.
10. Lambert SR, Lynn MJ, Reeves R, Plager DA, Buckley EG, Wilson ME. Is there a latent period for the surgical treatment of children with dense bilateral congenital cataracts? J AAPOS. 2006;10:30–6.

11. Birch EE, Cheng C, Stager DR Jr, Weakley DR Jr, Stager DR Sr. The critical period for surgical treatment of dense congenital bilateral cataracts. J AAPOS. 2009;13:67–71.
12. Rahi JS, Dezateux C. british congenital cataract interest group. congenital and infantile cataract in the United Kingdom: underlying or associated factors. Invest Ophthalmol Vis Sci. 2000;41:2108–14.
13. Haargaard B, Wohlfahrt J, Fledelius HC, Rosenberg T, Melbye M. A nationwide Danish study of 1027 cases of congenital/infantile cataracts: etiological and clinical classifications. Ophthalmology. 2004;111:2292–8.
14. Wirth MG, Russell-Eggitt IM, Craig JE, Elder JE, Mackey DA. Aetiology of congenital and paediatric cataract in an Australian population. Br J Ophthalmol. 2002;86:782–6.
15. Eckstein M, Vijayalakshmi P, Killedar M, Gilbert C, Foster A. Aetiology of childhood cataract in south India. Br J Ophthalmol. 1996;80:628–32.
16. Jain IS, Pillay P, Gangwar DN, Dhir SP, Kaul VK. Congenital cataract: etiology and morphology. J Pediatr Ophthalmol Strabismus. 1983;20:238–42.
17. SanGiovanni JP, Chew EY, Reed GF, Remaley NA, Bateman JB, Sugimoto TA, et al. Infantile cataract in the collaborative perinatal project: prevalence and risk factors. Arch Ophthalmol. 2002;120:1559–65.
18. Deweese MW. A survey of the surgical treatment of congenital cataracts. Am J Ophthalmol. 1962;53:853–8.
19. Yang ML, Hou CH, Lee JS, Liang YS, Kao LY, Lin KK. Clinical characteristics and surgical outcomes of pediatric cataract in Taiwan. Graefes Arch Clin Exp Ophthalmol. 2006;244:1485–90.
20. Kim KH, Ahn K, Chung ES, Chung TY. Clinical outcomes of surgical techniques in congenital cataracts. Korean J Ophthalmol. 2008;22:87–91.
21. Ledoux DM, Trivedi RH, Wilson ME Jr, Payne JF. Pediatric cataract extraction with intraocular lens implantation: visual acuity outcome when measured at age 4 years and older. J AAPOS. 2007;11:218–24.
22. Plager DA, Kipfer H, Sprunger DT, Sondhi N, Neely DE. Refractive change in pediatric pseudophakia: 6-year follow-up. J Cataract Refract Surg. 2002;28:810–5.

Clin Pediatr Endocrinol 2015; 24(3), 107–133

Original Article

Guidelines for Mass Screening of Congenital Hypothyroidism (2014 revision)

Mass Screening Committee, Japanese Society for Pediatric Endocrinology, and
Japanese Society for Mass Screening
Keisuke Nagasaki[1], Kanshi Minamitani[2], Makoto Anzo[3], Masanori Adachi[4], Tomohiro Ishii[5], Kazumichi Onigata[6], Satoshi Kusuda[7], Shohei Harada[8], Reiko Horikawa[9], Masanori Minagawa[10], Haruo Mizuno[11], Yuji Yamakami[12], Masaru Fukushi[13], and Toshihiro Tajima[14]

[1] *Division of Pediatrics, Department of Homeostatic Regulation and Development, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan*
[2] *Department of Pediatrics, Teikyo University Chiba Medical Center, Chiba, Japa*
[3] *Department of Pediatrics, Kawasaki City Hospital, Kawasaki, Japan*
[4] *Department of Endocrinology and Metabolism, Kanagawa Children's Medical Center, Kanagawa, Japan*
[5] *Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan*
[6] *Shimane University Hospital Postgraduate Clinical Training Center, Shimane, Japan*
[7] *Maternal and Perinatal Center, Tokyo Women's Medical University, Tokyo, Japan*
[8] *Division of Neonatal Screening, National Center for Child Health and Development, Tokyo, Japan*
[9] *Department of Endocrinology and Metabolism, National Center for Child Health and Development, Tokyo, Japan*
[10] *Division of Endocrinology, Chiba Children's Hospital, Chiba, Japan*
[11] *Departments of Pediatrics and Neonatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan*
[12] *Kanagawa Health Service Association, Kanagawa, Japan*
[13] *Sapporo IDL, Sapporo, Japan*
[14] *Department of Pediatrics, Hokkaido University School of Medicine, Sapporo, Japan*

Abstract. Purpose of developing the guidelines: Mass screening for congenital hypothyroidism started in 1979 in Japan, and the prognosis for intelligence has been improved by early diagnosis and treatment. The incidence was about 1/4000 of the birth population, but it has increased due to diagnosis of subclinical congenital hypothyroidism. The disease requires continuous treatment, and specialized medical facilities should make a differential diagnosis and treat subjects who are positive in mass screening to avoid unnecessary treatment. The Guidelines for Mass Screening of Congenital Hypothyroidism (1998 version) were developed by the Mass Screening Committee of the Japanese Society for Pediatric Endocrinology in 1998. Subsequently, new findings on prognosis and problems in the adult phase have emerged. Based on these new findings, the 1998 guidelines were revised in the current document (hereinafter referred to as the Guidelines). Target disease/conditions: Primary congenital hypothyroidism. Users of the Guidelines: Physician specialists in pediatric endocrinology, pediatric specialists, physicians referring patients to pediatric practitioners, general physicians, laboratory technicians in charge of mass screening, and patients.

Key words: congenital hypothyroidism, mass screening, guideline

Received: February 14, 2015 Accepted: March 24, 2015
Corresponding author: Toshihiro Tajima, Department of Pediatrics, Hokkaido University School of Medicine, N15, W7, Sapporo 060-0835, Japan E-mail: tajeari@hokudai.med.ac.jp

Introduction

Thyroid hormone is essential for neurodevelopment in the fetal and early neonatal phases. Congenital hypothyroidism (CH) causes neuronal migration disorder due to thyroid hormone deficiency, and serious CH delays psychomotor development. CH is preventable by early detection and treatment. Neonatal mass screening is performed worldwide and is useful for detection of CH (1, 2). Mass screening for CH started in 1979 in Japan and has been effective (3–5). The Guidelines for Mass Screening of Congenital Hypothyroidism were developed by the Japanese Society for Pediatric Endocrinology in 1998 (6, 7). Subsequently, the incidence of CH increased in several regions, and orthotopic slightly impaired synthesis also increased (8, 9). Details on the prognosis of adult CH and several genetic causes have also emerged. The American Academy of Pediatrics published clinical guidelines for CH in 2006 (10). The European Society for Paediatric Endocrinology held a meeting to reach a clinical and therapeutic consensus on CH to revise previous guidelines in 2010 (11) and published new guidelines in 2014 (12).

Based on new findings, we revised the guidelines for diagnoses and treatment of primary CH detected in neonatal mass screening. CH is described in the Guidelines as primary CH. Recommendations in the Guidelines include a "grade" and an "evidence level." The grade shows the strength of the recommendation based on findings in published studies, and the evidence level indicates the level of the study. Expert opinions are included in the Guidelines if there are no findings in studies or the opinions are considered to be appropriate.

Grade level

1. Major recommendation: Most patients receive benefits.
2. Minor recommendation: Many patients receive benefits. Requires consideration and selection based on the patient's conditions.

Evidence level

●○○ Low: Evaluation of case reports without controls

●●○ Medium: Cohort study without controls

●●● Cohort study with controls, nonrandomized comparative study

Consensus: Widely recognized ideas, even if a study has not been performed

1. Definition of Congenital Hypothyroidism

Recommendation

1-1. Primary congenital hypothyroidism (CH) should be used as a generic term for congenital thyroid hormone deficiency due to a morphological abnormality or dysfunction of the thyroid gland that develops in the fetal or perinatal stage. 1 (Consensus)

1-2. CH may be due to thyroid hormone deficiency. (Consensus)

1-3. Most cases of CH are persistent, but transient CH also occurs. Treatment should be the priority for hypothyroid patients. 1 (●●●)

1-4. CH includes subclinical CH. However, there is a lack of consensus on the definition of subclinical CH. Particularly in the neonatal stage, hypothyroidism may manifest suddenly, after which it is difficult to define such a case as subclinical CH. 2 (●○○)

Explanation

a. Congenital hypothyroidism

CH is a generic term for congenital thyroid hormone deficiency due to a morphological abnormality or dysfunction of the thyroid gland that develops in the fetal or perinatal stage. Thyroid hormone is essential for nerve myelination in the fetal, neonatal and infant stages. An insufficient thyroid hormone level causes irreversible mental retardation. In addition to direct involvement in bone maturation, thyroid hormones stimulate growth hormone secretion and enhance production of insulin-like growth factor-I. Therefore, thyroid