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Case Report

TUBA1A Mutation-Associated Lissencephaly: Case Report and Review of the Literature

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ABSTRACT

Lissencephaly is a disorder of neuronal migration resulting in abnormal cerebral cortical sulcation and gyration. Affected children present with microcephaly, developmental delay, and early-onset epileptic seizures. Recently, de novo missense mutations in the tubulin α-1A (*TUBA1A*) gene were identified as causing a distinctive radiologic phenotype comprising of posteriorly predominant lissencephaly with dysgenetic corpus callosum, cerebellar and brainstem hypoplasia, and more recently, polymicrogyria. We describe a 14-month-old girl with *TUBA1A* mutation-associated lissencephaly, and summarize the clinical and neuroradiologic findings of 19 cases in the literature.

Introduction

Lissencephalies comprise a rare subgroup of genetically distinct neurologic disorders of neuronal migration resulting in a paucity or absence of cerebral sulcation and gyration, along with abnormal histologic architecture of the cerebral cortex. Lissencephaly and pachygyria occur along an anatomic spectrum. In the most severe cases, no sulci (agyria) are evident, but in most patients, some gyri and sulci are present. Children affected with lissencephaly present in infancy with global developmental delay and early-onset epileptic infantile spasms.

Mutations in three autosomal genes, *LIS1*, *RELN*, and the *VLDL* receptor, and two X-linked genes, *DCX* and *ARX*, were observed to be associated with specific lissencephaly syndromes [1,2]. Recently, de novo missense mutations in the tubulin α-1A (*TUBA1A*) gene were identified in patients with a distinctive radiologic phenotype comprising posteriorly predominant lissencephaly with a dysgenetic corpus callosum and cerebellar and brainstem hypoplasia [3,4].

Thus far, 26 living patients and nine fetuses with de novo *TUBA1A* mutations have been described in literature [1,4-8]. We report on a patient with *TUBA1A*-associated lissencephaly and summarize the clinical details and neuroradiologic findings of all cases described in the literature.

Case Report

Our patient, a 14-month-old girl, first presented to the local hospital at age 10 weeks with respiratory syncytial virus-negative bronchiolitis and faltering growth. She was a born at term, with normal results of prenatal ultrasound scans, to healthy nonconsanguineous parents. Apart from early feeding difficulties, she was thought to be developing normally, with social smile at age 7 weeks. During her inpatient stay, she manifested tonic spasms affecting her trunk and limbs. Examination revealed a hypotonic baby with weak cry, microcephaly (occipitofrontal circumference, 35 cm; <0.4th percentile), mild dysmorphism (retrognathia, high-arched palate, and flattening of the occiput), and poor oropharyngeal coordination. She displayed marked stridor during feeding.

Initial normal investigations included a full blood count, electrolytes, liver and thyroid function, urine amino acids, organic acids, karyotype, and a DNA screen for Prader-Willi syndrome. Her electroencephalogram demonstrated florid epileptiform activity arising from multiple foci posteriorly (right > left), accompanied by bilateral slow wave activity. She underwent cranial magnetic resonance imaging at age 4 months, which revealed incomplete posterior lissencephaly primarily affecting the parieto-occipital cortices, along with cerebellar and brain stem hypoplasia. Testing for a *LIS1* gene mutation produced negative results. An electroretinogram produced normal results, but demonstrated significantly delayed visual evoked potentials bilaterally. She continued to exhibit an oropharyngeal lack of coordination with stridor, which improved remarkably after a gastrostomy at age 7 months. She manifested epileptic infantile spasms from age 7 months, poorly controlled on two antiepileptic drugs.

She was tested specifically for a *TUBA1A* mutation at age 1 year, and was observed to be positive for a heterozygous c.1205G>T (p.R402L) mutation. Both parents subsequently tested negative for the mutation. Mutations in the *RELN* and *VLDLR* genes were not tested in this patient. Further follow-up at age 4 months revealed continuing profound delay in development, with some head and upper

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Table 1. Summary of the clinical details of 19 children with lissencephaly-associated *TUBA1A* mutations

Age/Sex (Reference Number)	Mutation	OFC	Motor Signs	Clinical Features	
				Developmental Delay	Epilepsy
14 months/F*	c.1205G>T p.R402L	−4 S.D.	Unable to sit and bear weight	Not reaching for objects /no fix or follow, babbling	Present, with infantile spasms
7 years/M [1]	c.790C>T p.R264C	−4 S.D.	Spastic diplegia; walks independently	Speaks in short sentences	Absent
19 months/M [1]	c.790C>T p.R264C	−4 S.D.	Spastic tetraplegia	No language	Present, with early GTC
5.5 years/M [1]	c.1190T>C p.L397P	−4 S.D.	Spastic diplegia; walks with assistance	Few words	Absent
4.5 years/M [1]	c.1264C>T p.R422C	−3 S.D.	Spastic diplegia; walks independently	Speaks in short sentences	Absent
7 years/M [1]	c.1306G>T p.G436R	−3 S.D.	Spastic diplegia; walks independently	Speaks in short sentences	Absent
7 years/F [1]	c.1265G>A p.R422H	−4 S.D.	Spastic tetraplegia	Babbles	Present
1 year/M [6]	c.163G>A p.Glu55Lys	−7 S.D.	Unable to sit/stand or grab objects	Severe global delay	Present, with CPS/GTC
8.3 years F [6]	c.1204C>T p.R402C	−4 S.D.	Tetraplegia and central hypotonia	Severe global delay	Present
2.8 years/M [6]	c.1205G>T p.R402L	−3.5 S.D.	Tetraplegia and central hypotonia	Severe global delay	Present with focal seizures
9 years/M [6]	c.1265G>A p.R422H	−4 S.D.	Limb dystonia and axial hypotonia	Severe global delay	Present, with motor seizures
4 weeks/F [6]	c.1265G>A p.R422H	−3.5 S.D.	Not determined	Not determined	Present; generalized
2 years/M [4]	c.790C>T p.R264C	−4 S.D.	Mild; walks with assistance	Severe global delay	Absent
3.5 years/M [4]	c.790C>T p.R264C	−4.5 S.D.	Mild; walks with assistance	Severe global delay	Absent
2 years/M [4]	c.1205>A p.R402H	−3 S.D.	Spastic tetraplegia	Severe global delay	Present, with GTC
1 month/F [4]	c.562A>C p.I188L	−4 S.D.	Mild; walks with assistance	Severe global delay	Present, with tonic seizures
12 years/M [4]	c.1256C>T p.S419L	−1 S.D.	Spastic tetraplegia	Severe global delay	Present, with GTC
18 months/M [8]	c.629A>G p.Tyr210Cys	−3 S.D.	Spastic tetraplegia	No sitting or standing, no speech, reacts to sound	Present, with focal seizures
7 years/F [8]	c.13A>C p.Ile5Leu	−2 S.D.	Spastic diplegia and ataxia	Severe development delay	Present, with focal seizures
22 months/F [8]	c.13A>C p.Ile5Leu	−1 S.D.	Spastic diplegia, ataxia, and dystonia	Moderate developmental delay	Absent

Abbreviations:
CPS = Complex partial seizures
GTC = Generalized tonic-clonic seizures
F = Female
L = Left
M = Male
N/A = Not available
OFC = Occipitofrontal circumference
P>A = Posterior to anterior gradient
SBH = Subcortical band heterotropia
S.D. = Standard deviation
* Present case.

trunk control (nonweight-bearing), poor visual and social interactions, and occasional vocalization.

Discussion

Disorders of neuronal migration comprise rare genetic disorders of the central nervous system, characterized clinically by significant neurodevelopmental disability and severe epilepsy in childhood. Neurons that originate in the cortical ventricular and subventricular zone migrate radially to their final location [9]. Disorders of cell migration can be attributable to genetic and acquired causes. Many are the result of chromosomal deletions and gene mutations. The effect of these genetic defects as yet incompletely known, results in the failure of cell signaling systems that guide cell movements along radial glial fibers.

Disorders of neuronal migration are broadly classified according to their clinical and radiologic features, and include lissencephaly, focal cortical dysplasia, subcortical and periventricular heterotropia, schizencephaly, and polymicrogyria [10,11]. Lissencephaly, a subgroup of neuronal migration disorders, is characterized by an abnormally

Clinical Features	Neuroradiologic Findings				
Other Features	Cortical Gyration	Corpus Callosum	Ventricular Dilatation	Cerebellum	Brainstem
Retrognathia, high-arched palate, and flattened occiput	Agyria/pachygyria P>A	Mild hypoplasia	Moderate	Severe hypoplasia	Mild hypoplasia
Transient squint	Perisylvian pachygyria	Posterior agenesis	N/A	Normal	N/A
Transient squint and facial diplegia	Perisylvian pachygyria	Mild hypoplasia	N/A	Normal	N/A
Transient squint and facial diplegia	Perisylvian pachygyria	Posterior agenesis	N/A	Severe vermis dysplasia	N/A
None	Perisylvian pachygyria	Mild hypoplasia	N/A	Mild vermis hypoplasia	N/A
Transient squint and facial diplegia	Perisylvian pachygyria	Mild hypoplasia	N/A	Mild vermis hypoplasia	N/A
None	Posterior pachygyria	Mild hypoplasia	N/A	Mild vermis hypoplasia	N/A
Convergent squint and sloping forehead	Agyria/pachygyria, P>A	Partial agenesis	Trigone/occipital horn dilated	Severe vermis hypoplasia	Flattening isthmus/pons hypoplasia
Convergent squint nystagmus, long palpebral fissure, and long eyelashes, fingers, and toes	Agyria/pachygyria, P>A	Thin, absent rostrum, and splenial hypoplasia	Trigone/occipital horn dilated	Mild vermis hypoplasia	Mild pons hypoplasia
Nephrocalcinosis	Agyria/pachygyria, P>A	Hypoplasia	Lateral ventricles occipital/ anterior horns dilated	Mild vermis hypoplasia and retrocerebellar cyst	Mild pons hypoplasia
Lower limb contractures	Pachygyria with SBH	Partial agenesis	Lateral/fourth ventricle enlarged, with Dandy-Walker malformation	Severe vermis hypoplasia,	Severe pons hypoplasia
None	Pachygyria with SBH	Partial agenesis	Lateral/fourth ventricle enlarged	Moderate vermis hypoplasia	Mild pons hypoplasia
Facial diplegia	Pachygyria	Mild hypoplasia	Mild	Vermis hypoplasia	Brainstem hypoplasia
Transient squint	Pachygyria	Mild hypoplasia	Mild	Vermis hypoplasia	None
Facial diplegia squint	Agyria P>A	Thin, partial posterior agenesis	Severe	Vermis hypoplasia	Brainstem hypoplasia
Facial diplegia and squint	SBH	Posterior agenesis	Mild	Vermis hypoplasia	Brainstem hypoplasia
Facial diplegia and squint	Pachygyria, P>A	Mild hypoplasia	Severe	Vermis hypoplasia	Normal
Facial dysmorphism, retrognathia, simian crease, and spina bifida occulta	Agyria-pachygyria, A>P	Thin	N/A	Mild vermis hypoplasia	Mild hypoplasia
Pectus excavatum squint, and L facial nerve palsy	Perisylvian polymicrogyria	Thin	N/A	Normal	Mild hypoplasia
Absent	Perisylvian polymicrogyria	Hypoplastic splenium	N/A	Mild vermis hypoplasia	Mild hypoplasia

smooth surface of the cerebral cortex, attributable to a lack of normal cortical convolutions. Lissencephalies have been further classified on the basis of etiology and associated malformations into five groups: classic lissencephaly (type 1 lissencephaly), cobblestone lissencephaly (type 2 lissencephaly), X-linked lissencephaly with agenesis of the corpus callosum and abnormal genitalia, lissencephaly with cerebellar hypoplasia, and microlissencephaly [11,12].

LIS1 was the first gene to be correlated with human lissencephaly [13]. Mutations in the *LIS1* and *DCX* genes were attributed to approximately 85% of classic lissencephaly, and a smaller proportion of lissencephaly to *ARX*, *RELN*, and *VLDLR* gene mutations [14]. Mutations in *LIS1* are associated with abnormal sulcation, predominantly in the parietal and occipital cortices, whereas *DCX* lissencephaly is more pronounced in the frontal cortex [2]. Recently, mutations in the *TUBA1A* (α-tubulin complex) gene, located on chromosome 12q12-q14, which encodes for the α-tubulin protein, was correlated with phenotypes of the agyria-pachygyria band spectrum [4,6,15,16]. *TUBA1A* is a critical structural subunit of microtubules, and is transiently expressed during neuronal development [17]. The mechanisms of *TUBA1A* mutation

leading up to pathologic phenotypes remain unclear. Kumar et al. performed structural remodeling to suggest that mutations in this gene affect the overall tubulin architecture [14]. Poirier et al. screened 360 control individuals, but did not identify any known *TUBA1A* mutations in these individuals, which may suggest an absence of abnormal coding regions in normal populations and a genotype-phenotype association with these mutations [4]. So far, the clinical and radiologic features of 19 living patients, the radiologic findings of seven patients, and postmortem neuropathologic features of nine fetuses (at 21-35 weeks of gestation) have been described in the literature in association with *TUBA1A* mutations. We summarize the clinical and neuroimaging features of these 19 cases, along with our own, in Table 1.

All 19 children described in the literature demonstrated microcephaly and severe, gross motor delay. Of these, seven were able to walk independently or with assistance. Only two children, aged 7 years, were able to speak in short sentences, and in the remainder, speech was poor. Our patient is functioning at 2 months post term level, with a chronologic age of 14 months. Epilepsy, a prominent feature of lissencephaly, presents as infantile spasms or astatic-myoclonic seizures early on, evolving to complex epilepsy in later childhood, including atypical absence seizures, myoclonic and atonic drop seizures, partial complex seizures, and tonic and tonic-clonic seizures [18]. Our patient presented with epileptic spasms from age 7 months, poorly controlled with sodium valproate and levetiracetam. As indicated in Table 1, the cohort presented with varied seizure patterns, including generalized tonic-clonic, tonic, and focal seizures. Seven subjects had not manifested epileptic seizures at the time of this publication.

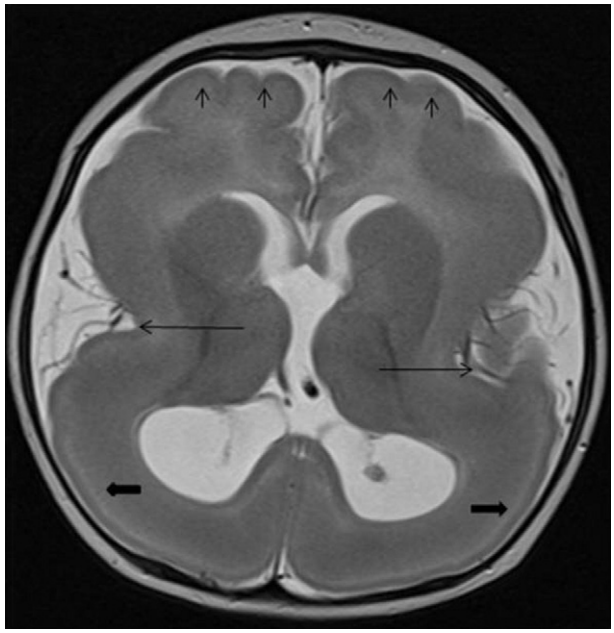

Figure 1. T_2-weighted axial magnetic resonance imaging of the brain demonstrates "smooth" brain with a "figure 8" configuration, attributable to the vertical orientation of sylvian fissures (long arrows). Hypoplasia of the anterior limb of the internal capsule, sparing of the anterior frontal lobes (short arrows), and a linear high signal underlying the cortical ribbon representing the cell-sparse zone (thick arrows) are evident.

The neuroradiologic features of classic lissencephaly involve agyria, pachygyria, a moderately thickened cortex along with poor development of the sylvian and rolandic fissures, a moderately thickened cortex, and white matter signal abnormalities [19]. Classic lissencephaly may sometimes be associated with dilatation of the lateral ventricles, mild hypoplasia of the corpus callosum, and persistent cavum septum pellucidum [20]. Mutations in the *TUBA1A* gene cause significant posterior, more than anterior, malformations of the gyral pattern (i.e., a posterior to anterior gradient). These malformations are combined with a partly dysgenetic corpus callosum, mild ventricular dilatation, and cerebellar vermian and brainstem hypoplasia, with the absence or hypoplasia of the anterior arm of the internal capsule [1,6]. So far, all cases with *TUBA1A* mutations, including ours, have been de novo in origin. Jansen et al. [8] described two siblings with a *TUBA1A* mutation (c.13A>C(p.lle5Leu)/Ex2) and with perisylvian polymicrogyria. These children were born to consanguineous parents, and the mother, who was asymptomatic, proved to be somatic-mosaic for the c.13A>C mutation [8]. The clinical and neuroradiologic features of these two children are also summarized in Table 1.

Kumar et al. summarized the cranial imaging features of 17 patients with *TUBA1A* mutations [14]. These features were divided into five radiologically distinct groups. The first two groups comprised recurrent mutations, all involving arginine residue at codon 402 (p.R402C and p.R402H). These neuroradiologic features were described previously in the literature, and are included in Table 1. The remaining three groups involved heterogeneous missense mutations throughout the gene (p.V137D, p.A270T, p.M377V, and p.R422H), novel heterozygous missense mutations (p.D218Y, p.N329S, p.M425K, and p.L92V), and a single patient with a novel de novo heterozygous mutation (p.R390C). The neuroradiologic features in the first group consisted of diffuse pachygyria with no areas of agyria, predominantly affecting posterior frontal, perisylvian, and parietal regions, malformed hippocampus and basal ganglia, an absent or nearly absent corpus callosum, a thin brainstem, and severe cerebellar hypoplasia. In the group with novel heterozygous missense mutations, the radiologic features comprised severe lissencephaly (near complete agyria, with pachygyria over the frontal poles) with cerebellar hypoplasia, severe ventriculomegaly, dysplastic basal ganglia, an absent corpus callosum, brainstem hypoplasia, and a relatively enlarged posterior fossa. The final category (i.e., a single patient with the novel de novo heterozygous mutation p.R390C) was described as manifesting a "simplified" gyral pattern (a mildly reduced number of gyri and shallow sulcal depth), with agenesis of corpus callosum and moderate cerebellar hypoplasia. Our patient was heterozygous for the c.1205G>T mutation, and demonstrated imaging features similar to those described earlier in the literature [6]. Bahi-Buisson et al. also described predominant perisylvian pachygyria as a radiologic finding in five of their six patients [1]. However, the rest of the patients, including ours (Figs 1 and 2), demonstrated agyria or pachygyria with a posterior to anterior gradient, along with moderate to severe hypoplasia of the corpus callosum, ventriculomegaly, and mild to severe cerebellar and brainstem hypoplasia.

Fallet-Bianco et al. described the neuropathologic findings of four fetuses with *TUBA1A* mutations (L286F, I238V, P263T, and R402C) who demonstrated consistent developmental anomalies in the cerebral gyration, corpus callosum, hippocampus, basal ganglia, cerebellum, and brainstem [5]. The abnormalities in the cerebral gyration were quite severe, and an unidentifiable sylvian fissure constituted a conspicuous finding in all fetuses. Lecourtois et al. described the neuropathologic features of a fetus at 36 weeks of gestation (c.908T>G) with pachygyria (a posterior to anterior gradient), short and vertically oriented sylvian fissures, severe ventriculomegaly, a thin corpus callosum (macroscopically observed only in the anterior part), a thin brainstem (a flattened pons and medulla), and a hypoplastic cerebellum [7].

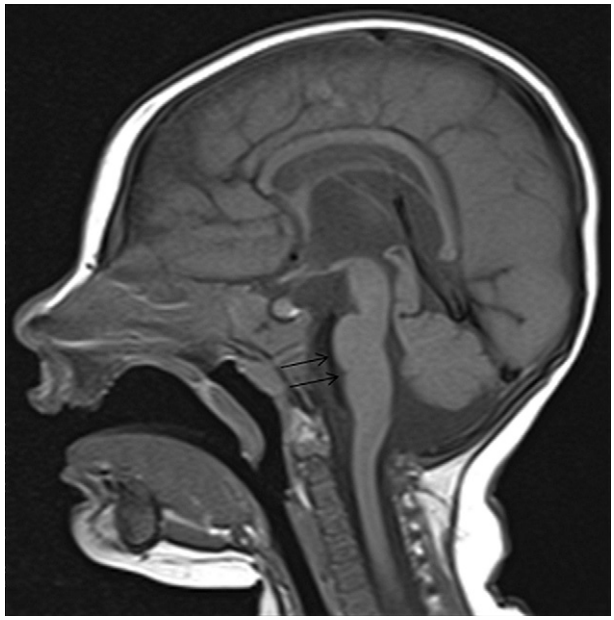

Figure 2. T_1-weighted sagittal magnetic resonance imaging demonstrates brainstem hypoplasia (loss of the pontine bulge), cerebellar hypoplasia, and a thin corpus callosum.

The phenotypic associations of *TUBA1A* mutations have not been fully characterized. Most patients, as demonstrated in Table 1, are microcephalic, appear mildly dysmorphic, and demonstrate transient to fixed strabismus and facial diplegia. One patient manifested a long palpebral fissure, long eyelashes, long fingers and toes, and spina bifida occulta with simian creases. Our patient exhibited retrognathia, a high-arched palate, and a flattened occiput. Her stridor, which was also evaluated by ear, nose, and throat specialists, was attributed primarily to a central cause, with a mild degree of laryngomalacia.

In conclusion, mutations in the *TUBA1A* gene were recently described in patients who presented with lissencephaly, which varies from a perisylvian to a posteriorly predominant pachygyria, along with ventricular dilation and callosal, cerebellar, and brainstem hypoplasia, and more recently, polymicrogyria. These radiologic features, combined with global development delay and epilepsy, should prompt the clinician to perform *TUBA1A* gene mutation testing. If the results are positive, the parents must be tested for future genetic counseling. We emphasize that the associated radiologic and phenotypic features will help refine our understanding of "lissencephaly syndromes" associated with *TUBA1A* mutations.

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