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Case Series

Radiology Section

# The Different Faces of Tubulinopathies: A Series of Three Cases with MRI Findings

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## ABSTRACT

Tubulin genes encode for microtubules, which are involved in a wide range of cellular functions and neurological development. Tubulinopathies are a spectrum of mutations in these genes that often present as complex congenital, non progressive brain malformations. Clinical symptoms may include developmental delay, cognitive impairments and a wide spectrum of structural brain anomalies. Tubulin Alpha 1a (TUBA1A), Tubulin Beta 2b (TUBB2B), Tubulin Beta 3 (TUBB3), and Tubulin Beta 4a (TUBB4A) significantly affect microtubule formation and exhibit a wide range of imaging findings. The present case series found cortical malformations in two cases; one case showed cerebellar dysmorphism, and all cases showed corpus callosum thinning. The current case series is necessary to illustrate the broad clinico-radiological spectrum of TUBA1A, TUBB2B and TUBB3 mutations. The case series aimed to highlight the diverse and common Magnetic Resonance Imaging (MRI) findings associated with these disorders by detailing three distinct cases. By analysing the findings from these cases, the authors aimed to deepen the understanding of these diseases, facilitate early identification, and ultimately improve management strategies for affected individuals.

**Keywords:** Cerebellar dysmorphism, Corpus callosum thinning, Magnetic resonance imaging, Tubulin genes

## INTRODUCTION

Tubulinopathies represent a complex spectrum of brain malformations caused by mutations in genes encoding α and β-tubulin, which are essential for critical processes such as neuronal migration and axonal guidance [1]. Current clinical practice often struggles to diagnose or classify these conditions due to their phenotypic variability. By highlighting pathognomonic MRI signs, such as the "absent anterior limb of the internal capsule," the authors aimed to equip clinicians with the diagnostic patterns needed to facilitate early genetic testing and improve long-term patient management.

## CASE SERIES

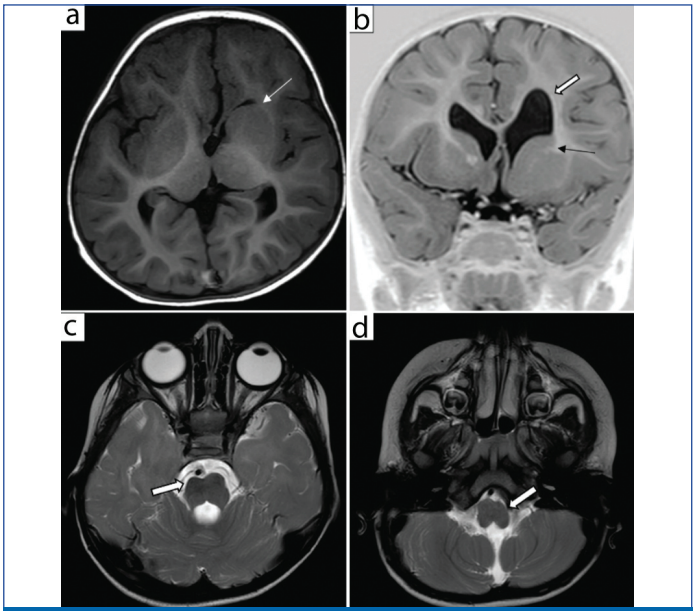
### Case 1

An 18-month-old female came to the Outpatient Department with complaints of evolving spastic cerebral palsy over a period of nine months. The mother noticed that the child was unable to fixate eyes, creep, or crawl. Clinical examination revealed delayed achievement of developmental milestones, nystagmus and visual impairment. No history of preterm birth or Neonatal Intensive Care Unit (NICU) admission was obtained. Brain MRI was performed [Table/Fig-1]. Genetically, targeted sequencing revealed a missense mutation of the TUBB3 gene.

### Case 2

A 12-year-old male came to the Outpatient Department with complaints of aggressive and irritable behaviour for 2-3 years. Clinical examination revealed head size 49 cm {<-3 Standard Deviation (SD)}, abnormal ears, intellectual disability and microcephaly; however, developmental milestones were normally achieved.

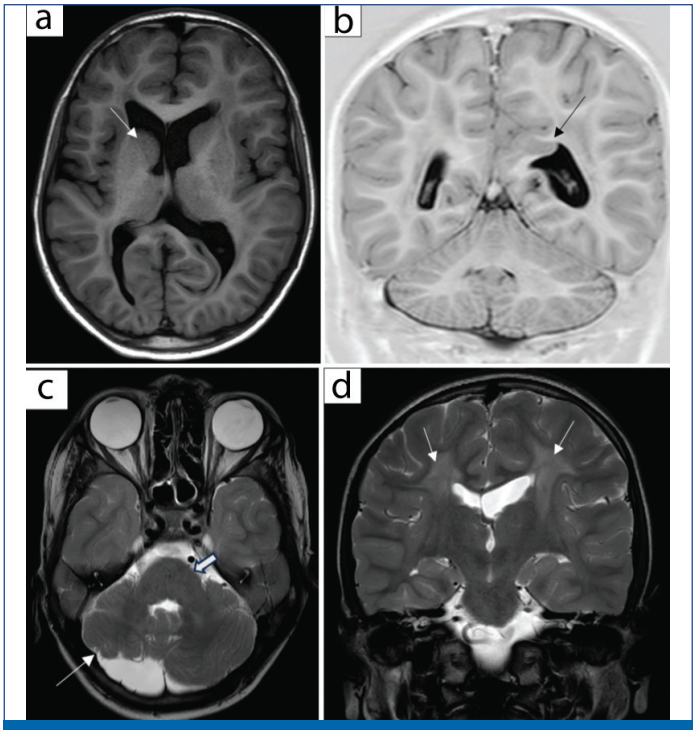
Bilateral squint was present. There was a history of bilateral cataract surgery performed at 1.5 years of age. No history of preterm birth or NICU admission was present. An Electroencephalography (EEG) study revealed neuronal hyperexcitability. Brain MRI was performed [Table/Fig-2]. Genetic sequencing revealed a mutation of the TUBA1A gene.



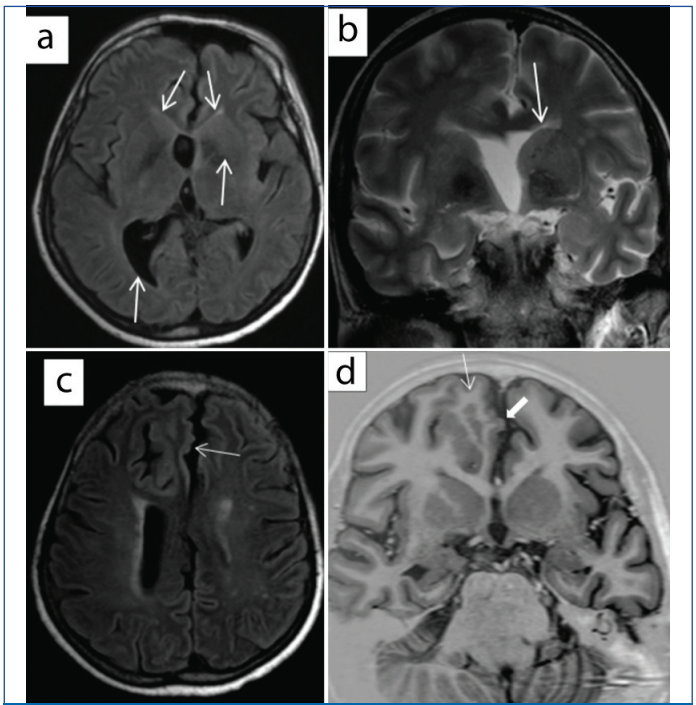

**[Table/Fig-1]:** a) T1 axial showing incomplete fusion between the head of left caudate nucleus and putamen with an indistinct anterior limb of internal capsule (arrow); b) T1 Coronal Inversion Recovery (IR) showing indistinct left anterior limb of internal capsule (black arrow) with asymmetric dilatation of lateral ventricles (L >R) (white arrow); c) T2 axial showing dysmorphic brainstem with asymmetric hypoplasia of right hemipons with flattening of pontine belly (arrow); d) T2 axial showing asymmetric hypoplasia of left hemimedulla (arrow).

### Case 3

A 52-year-old female, known case of seizure disorder since the age of 15 years was admitted with complaints of daily 2-3 episodes of generalised tonic-clonic seizures and progressive decline in sensorium for the past week. No history of fever, recent head trauma, or drug overdose. There was increased drowsiness, reduced responsiveness to verbal stimuli, and decreased oral intake. She had no recent changes in her anti-epileptic medications (Clobazam) and was known to be irregular with her drug compliance. MRI brain was done [Table/Fig-3,4]. Genetically, targeted sequencing revealed a mutation of the TUBB2B gene.




**[Table/Fig-2]:** a) T1 axial showing an indistinct right anterior limb of internal capsule (arrow); b) T1 Coronal IR showing closed lip Schizencephaly in left precuneus (arrow); c) T2 axial showing dysmorphic brainstem with asymmetric hypoplasia of left hemi-pons with flattening of pontine belly (thick white arrow) and asymmetric hypoplasia of right cerebellar hemisphere (white thin arrow); d) T2 coronal showing bilaterally symmetrical periventricular and deep white matter T2 hyperintensities (arrow).




**[Table/Fig-3]:** a) Fluid-Attenuated Inversion Recovery (FLAIR) axial showing indistinct left anterior limb of the internal capsule. Decreased size of the frontal horns of the left lateral ventricles with prominence of occipital horns (arrows); b) T2 Coronal sequence showing hooking of the head of the left caudate into the lateral ventricle (arrow) and absent septum pellucidum; c) FLAIR axial with polymicrogyria along the right superior frontal gyrus (arrow); d) T1 coronal IR showing right frontal polymicrogyria (block arrow) and nodular heterotopia (thin arrow).

## DISCUSSION

Tubulins form microtubules, filamentous structures critical to mitosis, axon navigation, and neuronal migration, all key factors in brain development [1]. Thus, mutations in tubulin genes can alter the normal function and structure of microtubules, leading to complex congenital and non progressive disorders of brain development characterised by severe brain malformations [2].

Among tubulin-encoding genes, diseases caused by TUBB3 mutations are rare, and only 15 TUBB3 mutations have been identified [3]. TUBB3 encodes beta tubulin isotype 3, a neuron specific component of microtubules. Heterozygous missense mutations in TUBB3 have been reported to be associated with decreased microtubule stability [4]. Clinical symptoms resulting from hypoplasia of the oculomotor nerve include esotropia, nystagmus, and paralytic eye movement disorders, such as Congenital Fibrosis of the Extraocular Muscles (CFEOM3) [5]. Patients show gross motor delays associated with axial hypotonia, sensorimotor polyneuropathy and intellectual disability [4].

The most consistent feature is dysmorphic basal ganglia, present in up to 75% of cases. A key sign associated with this is the "Absent Anterior Limb of Internal Capsule (ALIC) sign", which refers to the dysgenesis or agenesis of the anterior limb of the internal capsule, leading to a fused appearance of the caudate and putamen and a hooking appearance of the caudate nucleus on the lateral ventricle, which was also seen in all of our cases [6]. In a review by Romaniello R et al., Mutations in seven genes encoding alpha-tubulin (TUBA1A), beta-tubulin (TUBB2A, TUBB2B, TUBB3, TUBB4A, TUBB5) and gamma-tubulin (TUBG1) isoforms have been associated with a wide and overlapping range of brain malformations or "Tubulinopathies" [7]. Multiple studies have shown that tubulinopathies have a few recognisable and sometimes characteristic imaging findings [Table/Fig-5] [6,8,9].

Tubulinopathies are distinguished from Lissencephaly-1 (LIS1)-related lissencephaly by the pathognomonic presence of dysmorphic, fused basal ganglia and asymmetric brainstem hypoplasia. Unlike congenital infections such as Zika virus, which may present with intracranial calcifications or periventricular cysts, tubulin-related disorders show structural deep grey matter and cerebellar malformations [10].

Genetic counselling is a critical component of managing tubulinopathies to determine recurrence risk for future pregnancies, as the genetic mutation is autosomal dominant in all cases and a de novo variant in 95% of cases [6]. However, few cases of parental germline mosaicism have been reported, which increases the risk of having another affected child [6]. Ultimately, pharmacological, surgical and rehabilitative therapies are required to optimise functional outcomes as patient's age from childhood into adulthood.

## CONCLUSION(S)

Tubulinopathies form a group of underdiagnosed cortical malformations, and MRI serves as an essential tool in their evaluation. As awareness of these disorders grows, so does the necessity for clinicians to recognise the diverse clinical and imaging manifestations. Future studies should focus on larger cohorts to establish clearer diagnostic criteria and explore potential therapeutic avenues to improve outcomes for individuals affected by these complex conditions.

| MRI Feature | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| **Age/Gender** | **18-month-old/Female** | **12-year-old/Male** | **52-year-old/Female** |
| Clinical presentation | Spastic cerebral palsy, delayed developmental milestones, and visual impairment | Aggressive behaviour, intellectual disability, microcephaly, bilateral congenital cataract | Seizure disorder since childhood, altered sensorium |
| Basal ganglia | Fusion of the left head of caudate & lentiform nucleus; indistinct anterior limb of internal capsule [Table/Fig-1a] | Partial fusion of the right head of the caudate & lentiform nucleus; indistinct anterior limb of the internal capsule [Table/Fig-2a] | Fusion of left head of the caudate & lentiform nucleus; indistinct anterior limb of internal capsule [Table/Fig-3a,b] |
| Ventricles | Asymmetric dilatation (L>R) [Table/Fig-1b] | Asymmetric dilatation (L>R) [Table/Fig-2b] | Asymmetric dilatation (R>L) [Table/Fig-3a] |

| | | | |
|---|---|---|---|
| Brainstem | Asymmetric hypoplasia of right hemipons (flattened belly); hypoplasia of left hemimedulla [Table/Fig-1c,d] | Asymmetric hypoplasia of left hemipons; flattening of pontine belly; asymmetric hypoplasia of right cerebellar hemisphere [Table/Fig-2c] | Mild thinning of left cerebral peduncle secondary to hemispheric volume loss |
| Corpus callosum | Mild thinning | Mild thinning | Mild thinning |
| Cortical malformations | - | Focal cortical thickening & polymicrogyria in left precuneus along subparietal sulcus- closed-lip schizencephaly [Table/Fig-2b] | Polymicrogyria along right superior frontal gyrus; fusion of right superior frontal gyrus with cingulate; nodular heterotopia in right superior frontal gyrus & left insular cortex [Table/Fig-3c,d] |
| White matter | - | Bilateral (L>R) deep & periventricular white matter hyperintensities; mild paucity [Table/Fig-2d] | Mild hemispheric volume loss (L<R) |
| Midline structures | - | - | Absent septum pellucidum; hypoplastic falx cerebri with interdigitating frontal gyri [Table/Fig-3b] |
| Cerebellum | - | Right cerebellar hemisphere hypoplasia [Table/Fig-2c] | - |
| Other notable findings | - | - | Holoprosencephaly variant |
| Gene mutation | TUBB3 | TUBA1A | TUBB2B |

**[Table/Fig-4]:** Comparative findings in three cases of tubulinopathies.

| Author and year | Study design | Primary gene(s) studied | No. of patients | Notable findings |
|---|---|---|---|---|
| Bahi-Buisson N et al., (2014) [6] | Cohort Study / Case Series | Multiple (TUBA1A, TUBB2B, TUBB3, TUBB5) | 106 | Dysmorphic basal ganglia are the hallmark of tubulinopathies (found in 75% of cases) and are present in 100% of central pachygyria and polymicrogyria-like cortical dysplasia and simplified gyral malformation syndromes. Tubulinopathies are also characterised by a high prevalence of corpus callosum agenesis (32/80; 40%), and mild to severe cerebellar hypoplasia and dysplasia (63/80; 78.7%). |
| Poirier K et al., (2013) [8] | Case series | TUBB3 | 16 | They report the discovery of six novel missense mutations in the TUBB3 gene, including one fetal case and one homozygous variant in nine patients who all share cortical disorganisation and axonal abnormalities associated with pontocerebellar hypoplasia, but no ocular motility defects. |
| Jansen AC et al., (2011) [9] | Case series | TUBA1A | 25 | Two novel heterozygous missense mutations in TUBA1A were identified: c.629A>G (p.Tyr210Cys) occurring de novo in a boy with lissencephaly, and c.13A>C (p.Ile5Leu) affecting 2 sisters with polymicrogyria whose mother presented somatic mosaicism for the mutation. |

**[Table/Fig-5]:** Comparison of similar studies [6,8,9].

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