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TUBB3 GENE MUTATION ARG262HIS BEYOND CRANIAL DYSINNERVATION: EVIDENCE OF MALFORMATION OF CORTICAL DEVELOPMENT

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ABSTRACT

Background: Pathogenic variants in TUBB3 are associated with a spectrum of neurodevelopmental disorders, including congenital cranial dysinnervation disorders and tubulinopathies affecting neuronal migration.

Methods and Result: We report a preterm female infant with a heterozygous pathogenic TUBB3 variant (c.785G>A; p. Arg262His) presenting in the neonatal period with severe respiratory distress, feeding difficulty, cranial nerve dysfunction, and multiple congenital contractures. Brain MRI demonstrated malformations of cortical development, including a simplified gyral pattern, cortical thickening, basal ganglia dysplasia with fusion of the caudate and putamen, thalamic asymmetry, distortion of the interhemispheric fissure, inferior vermian hypoplasia, and thinning of the corpus callosum. Ophthalmologic findings included absent blinking and early corneal involvement.

Conclusion: This case expands the phenotypic spectrum of the TUBB3 p.Arg262His variant by demonstrating significant malformations of cortical development and highlighting severe early cranial nerve dysfunction with vision-threatening ocular surface complications.

KEYWORDS: TUBB3, Arg262His, Tubulinopathy, Basal ganglia dysplasia, Congenital cranial dysinnervation disorders

INTRODUCTION

The TUBB3 gene encodes a neuron-specific β-tubulin isotype critical for microtubule function, neuronal migration, and axonal guidance [1]. Pathogenic variants in TUBB3 are associated with a spectrum of disorders collectively known as tubulinopathies, ranging from congenital cranial dysinnervation disorders (CCDDs) to malformations of cortical development [2,3,8].

The recurrent TUBB3 variant c.785G>A (p.Arg262His) has been described as causing a recognizable syndrome characterized by congenital fibrosis of the extraocular muscles type 3, facial weakness, joint contractures, and early-onset peripheral neuropathy [4]. Neuroimaging findings in association with this variant are variable and generally less emphasized compared to clinical features [5,4].

We report a neonatal case with TUBB3 p.Arg262His demonstrating significant structural brain abnormalities and severe early cranial nerve dysfunction, thereby expanding the known phenotypic and neuroimaging spectrum.

CASE

The patient is a preterm female infant born at 35 weeks' gestation from a twin pregnancy via emergency cesarean section due to oligohydramnios and fetal distress. Her birth weight was 2.35 kg. She had poor adaptation to extrauterine life at birth and required admission to the neonatal intensive care unit for respiratory distress.

On the second day of life, she required mechanical ventilation and was noted to have a difficult airway, prompting transfer to a tertiary care center, where she remained hospitalized for 87 days. During this period, she was managed for respiratory distress, jaundice, and feeding intolerance attributed to poor sucking.

Investigations revealed a small patent ductus arteriosus on echocardiography, a normal abdominal ultrasound, and mild left ventriculomegaly on cranial ultrasound. EEG and brain magnetic resonance spectroscopy were normal, and karyotyping showed a normal 46, XX complement.

Family history was unremarkable, with non-consanguineous parents, six healthy siblings, and a healthy co-twin.

On examination, the infant appeared irritable and dysmorphic, with multiple congenital contractures involving the facial musculature, sternocleidomastoid muscle, and both upper and lower limbs. She has inability to blink, fix or follow target with left eye corneal ulceration (Figure 1). She exhibited a fixed inward posture of the thumbs. Growth

parameters were below the second percentile. poor sucking, generalized hypotonia with superimposed spasticity, and brisk deep tendon reflexes,
She was discharged on orogastric tube feeding; however, this was discontinued after two weeks due to caregiver difficulty. Subsequently, she developed recurrent choking and aspiration episodes, feeding-associated irritability, and failure to thrive, with weight decreasing from 2.8 kg to 2.6 kg over one month. There were no seizures or developmental regression.

Genetic Study

Whole exome sequencing identified a heterozygous pathogenic variant in the TUBB3 gene (c.785G>A; p.Arg262His). The TUBB3 p.Arg262His (c.785G>A) variant is a well-documented pathogenic mutation. Utilizing ACMG-AMP criteria, this variant fulfills multiple strong and moderate lines of evidence. PM1: The Arg262 residue is located in a critical functional domain responsible for the interaction between microtubules and kinesin motor proteins. It acts as a mutational hotspot, with other variants at this codon (e.g., p.Arg262Cys) also established as pathogenic. PS3: In vitro and in vivo functional studies demonstrate that mutations at Arg262 do not prevent tubulin heterodimer assembly or incorporation into the microtubule polymer, but rather cause altered microtubule dynamics and severely impair the binding of kinesin motors, leading to defective axonal transport and guidance. PM2: The variant is exceptionally rare and absent from large population databases like gnomAD. PP3: Multiple in silico prediction tools (e.g., PolyPhen-2, SIFT, MutationTaster) unanimously predict a deleterious effect on protein function, which is consistent with the extreme evolutionary conservation of this residue down to yeast. PM5: Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before. Based on the aggregate evidence, this variant is definitively classified as Pathogenic, acting via a dominant-negative mechanism to cause the severe neurological and developmental manifestations characteristic of TUBB3-related tubulinopathies. The p.Arg262His missense variant alters a highly conserved residue critical for microtubule dynamics and kinesin interaction, leading to disrupted axonal guidance.

Neuroimaging Findings

Brain magnetic resonance imaging demonstrated multiple abnormalities consistent with a malformation of cortical development. There was a simplified gyral pattern predominantly affecting the right cerebral hemisphere, with associated cortical thickening along the right sylvian fissure. The basal ganglia appeared dysmorphic, with fusion of the caudate nucleus and putamen, and the thalami were mildly asymmetric. In addition, there was distortion of the anterior interhemispheric fissure. Posterior fossa evaluation revealed mild inferior vermian hypoplasia, and the corpus callosum was noted to be thin. (Figure 2) These findings are consistent with disrupted neuronal migration and cortical organization as described in tubulinopathies [2].

Figure 1: Image of the face shows left eye keratopathy due to impaired blinking.

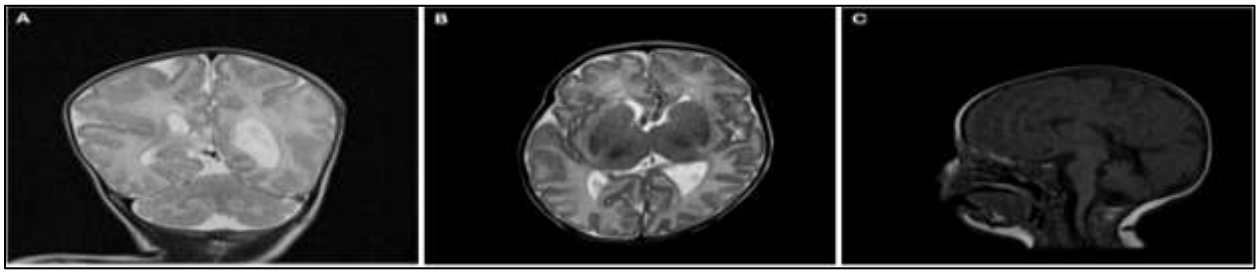

Figure 2: Brain MRI findings **A:** Coronal T2-weighted image demonstrating a mildly simplified gyral pattern in the right hemisphere, with cortical thickening along the right Sylvian fissure. **B:** Axial T2-weighted image showing enlarged, rounded basal ganglia with apparent fusion of the caudate nucleus and putamen. The thalami are mildly

asymmetric, and there is distortion of the anterior interhemispheric fissure. **C:** Sagittal T1-weighted image demonstrating mild inferior vermian hypoplasia and thinning of the corpus callosum.

DISCUSSION

TUBB3-related disorders result from disruption of microtubule dynamics, affecting both neuronal migration and axonal guidance [1,2]. The phenotypic spectrum is broad and varies according to the specific mutation, ranging from isolated cranial nerve dysfunction to complex malformations of cortical development [2,3].

The p.Arg262His variant has been consistently associated with a recognizable syndrome characterized by cranial dysinnervation, facial weakness, joint contractures, and peripheral neuropathy [4]. In these cases, neuroimaging abnormalities have been reported but are typically less prominent [5,4].

In contrast, the present case demonstrates clear and extensive malformations of cortical development, including simplified gyration, cortical thickening, and basal ganglia dysplasia. These findings are more characteristic of severe tubulinopathies and overlap with phenotypes described in other tubulin gene mutations [6,7,2]. Basal ganglia fusion observed in this case represents a hallmark imaging feature of tubulinopathies, though it has not been prominently emphasized in association with the Arg262His variant [2]. The asymmetric cortical involvement further supports a neuronal migration disorder pattern.

Clinically, this patient exhibited severe early neonatal manifestations, including respiratory distress, feeding difficulty, and cranial nerve dysfunction, highlighting the variability and potential severity of this condition [4].

An additional notable aspect of this case is the early and severe ocular surface involvement, characterized by absent or markedly impaired blinking and subsequent corneal pathology. While ocular motility abnormalities are well described in TUBB3-related disorders, these typically reflect extraocular muscle fibrosis and cranial dysinnervation rather than anterior segment complications [3]. In contrast, impaired blinking in this patient likely reflects dysfunction of cranial nerves responsible for eyelid closure, particularly the facial nerve, resulting in inadequate corneal protection. This mechanism predisposes to exposure keratopathy, recurrent infection, and progressive corneal damage, as observed in our patient at a very early age. The early onset and severity of corneal involvement suggest a more profound degree of cranial nerve dysfunction and highlight an important, potentially vision-threatening complication that may be underrecognized in TUBB3 p.Arg262His syndrome.

Furthermore, the combination of structural brain abnormalities and severe cranial nerve dysfunction in this case may indicate a more severe end of the phenotypic spectrum. Early ocular surface disease may therefore serve as a clinical marker of disease severity, warranting prompt ophthalmologic evaluation and proactive management to prevent irreversible visual impairment.

Together, these findings suggest that the phenotypic spectrum of the TUBB3 p.Arg262His variant may be broader than previously recognized, particularly with respect to structural brain abnormalities and early severe cranial nerve involvement.

CONCLUSION

This case expands the phenotypic and neuroimaging spectrum of the TUBB3 p.Arg262His variant by demonstrating significant malformations of cortical development and highlighting severe early cranial nerve dysfunction with vision-threatening ocular surface complications. Recognition of this broader and potentially more severe presentation is essential for early multidisciplinary management and appropriate genetic counseling.

REFERENCES

1. Nugent AA, Kolpak AL, Engle EC. Human disorders of axon guidance. Curr Opin Neurobiol. 2012;22(5):837-43.
2. Poirier K, Saillour Y, Bahi-Buisson N, Jaglin XH, Fallet-Bianco C, Nabbout R, et al. Mutations in the neuronal ß-tubulin subunit TUBB3 result in malformation of cortical development and neuronal migration defects. Hum Mol Genet. 2010;19(22):4462-73.
3. Whitman MC, Engle EC. Ocular congenital cranial dysinnervation disorders (CCDDs): insights into axon growth and guidance. Hum Mol Genet. 2017;26(R1):R37-R44.
4. Whitman MC, Barry BJ, Robson CD, Facio FM, Van Ryzin C, Chan WM, et al. TUBB3 Arg262His causes a recognizable syndrome including CFEOM3, facial palsy, joint contractures, and early-onset peripheral neuropathy. Hum Genet. 2021;140(12):1709-31.
5. Wang D, Jia HY, Liang Y, Ma Q, Chang QL, Zhang RR, et al. Clinical and MRI differences in congenital fibrosis of extraocular muscles patients with KIF21A and TUBB3 variants. Jpn J Ophthalmol. 2026;70(1):48-61.
6. Cederquist GY, Luchniak A, Tischfield MA, Peeva M, Song Y, Menezes MP, et al. An inherited TUBB2B mutation alters a kinesin-binding site and causes polymicrogyria, CFEOM and axon dysinnervation. Hum Mol Genet. 2012;21(26):5484-99.
7. Jurgens JA, Barry BJ, Lemire G, Chan WM, Whitman MC, Shaaban S, et al. Novel variants in TUBA1A cause congenital fibrosis of the extraocular muscles with or without malformations of cortical brain development. Eur J Hum Genet. 2021;29(5):816-26.
8. Jia H, Ma Q, Liang Y, Wang D, Chang Q, Zhao B, et al. Clinical and genetic characteristics of Chinese patients with congenital cranial dysinnervation disorders. Orphanet J Rare Dis. 2022;17(1):431.