

CLINICAL REPORT

Diagnosis and treatment of MN1 C-terminal truncation syndrome

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Abstract

Background: MN1 C-terminal truncation (MCTT) is a rare syndrome; only 27 cases have been reported. We report the first case of an 8-year-old girl with MCTT syndrome complicated with moderate obstructive sleep apnea (OSA).

Methods: MCTT syndrome was diagnosed by whole-exome sequencing (WES) and validated by Sanger sequencing. The patient received 2 years of treatment with continuous positive airway pressure (CPAP) to relieve sleep apnea and hypoxia, and a reverse sector fan-shaped expander for maxillary expansion.

Results: WES revealed a de novo MN1 variant, c.3760C>T (p.[Q1254*]). An arachnoid cyst was found in the right occipital brain. The patient presented mild symptoms of classic MCTT syndrome. The patient did not experience hearing loss and only mild intellectual disability. Radiological examinations showed cleft secondary palate, narrow upper arch, narrow upper airway, and mandibular skeletal retrusion. Polysomnography indicated moderate OSA, with an apnea/hypopnea index of 6.8, which decreased to 1 after CPAP during the night. Two-year maxillary expansion widened the upper arch, and the cleft secondary palate became visible. The mandible moved forward spontaneously, resulting in the improvement of profile and upper airway widening. General physical conditions, such as motor delay, muscle weakness, and developmental delay, were significantly improved two years later.

Conclusion: In conclusion, we discovered a MN1 variant [NM_002430.2: c.3760C>T, p.Q1254*] that causes mild MCTT symptoms compared to other MN1 variants. For patients with MCTT complicated with OSA, multidisciplinary combination therapy can improve maxillofacial development, widen the upper airway and relieve sleep apnea, improving the general physical condition.

KEYWORDS

MN1 C-terminal truncation syndrome, obstructive sleep apnea, sequencing, variant

1 | INTRODUCTION

MN1 C-terminal truncation (MCTT) syndrome was defined by Mak, Doherty, et al. (2020). Only 27 cases have been reported to date (Mak, Doherty, et al., 2020; Miyake et al., 2020; Tian et al., 2021; Zhao et al., 2021). Clinical symptoms include characteristic facial and brain imaging features, cranial shape defects, hypotonia, and developmental and motor delay. The main treatment approach is to address the developmental delay and cardiovascular diseases and refer the patient to a stomatologist for maxillofacial malocclusion (Mak, Fung, et al., 2020). There are no reports on the curative effect of this approach for MCTT syndrome.

MCTT syndrome is caused by C-terminal truncation mutation of *MN1*. *MN1*, which is located at 22q12.1, encodes a transcriptional co-regulator. In humans, it comprises two exons and encodes 1320 amino acid residues. *MN1* was first reported in meningioma patients and is expressed in various tissues and tumors (Lekanne Deprez et al., 1995). In addition, it is related to hematological malignancies, especially, acute myeloid leukemia (Grosveld, 2007). Mak et al. found that all *MN1* mutations are located in the terminal exon or the extreme 3' region of exon 1 and lead to the expression of a C-terminally truncated protein. To date, 15 mutation sites in *MN1* have been found to cause MCTT syndrome (Mak, Doherty, et al., 2020; Miyake et al., 2020; Tian et al., 2021; Zhao et al., 2021). However, the pathogenesis of MCTT syndrome is unclear. The relationships between gene mutations and phenotypes have not been established.

Obstructive sleep apnea/hypopnea syndrome (OSA) is caused by repeated partial or complete collapse of the upper airway, increasing airflow resistance in the airway during sleep. The main symptoms are snoring, daytime sleepiness, inattention, and other sleep disorders. It can cause developmental delay, mood disorder, and intelligence decline in children. Moreover, it increases the risk of death and seriously endangers the physical and mental health of patients (Bue et al., 2020; Savini et al., 2019). The main treatments for OSA include continuous positive airway pressure (CPAP), drug therapy, oral appliance, and surgical reconstruction of the upper airway (Bue et al., 2020; Ngiam et al., 2013). None of the MCTT syndrome patients reported to date presented OSA symptoms.

Here, we report a case of MCTT complicated with OSA. We discuss the *MN1* mutation, symptoms, treatment, and changes in the patient after 2 years of treatment with the aim to provide a reference for the diagnosis and treatment of patients with MCTT syndrome.

2 | MATERIALS AND METHODS

2.1 | DNA preparation and genetic analysis

We collected 5 ml of peripheral venous blood after obtaining written informed consent from the patient. DNA was extracted from peripheral leukocytes (Ezup Column Blood Genomic DNA Purification Kit, Sangong Bioengineering, Shanghai, China). Whole-exome sequencing (WES) was performed as previously reported (Miyake et al., 2015). Candidate variants were validated by Sanger sequencing (Sangong Bioengineering). This study was approved by the ethics committee of China Medical University, Hospital of Stomatology (approval No.: 2021–20).

2.2 | Clinical examination

Posteroanterior and lateral cephalography, panoramic radiography, cone beam computed tomography, facial and intraoral imaging, intraoral scanning, and plaster modeling were carried at China Medical University, Hospital of Stomatology. In addition, the patient was monitored by polysomnography. General physical examination, including basic examination; ultrasound of the liver, gallbladder, pancreas, spleen, kidneys, and brain; echocardiography; computed tomography of the chest and upper respiratory tract; and brain MRI, and developmental evaluation were performed at Shengjing Hospital, China Medical University.

2.3 | Treatment

An individualized reverse sector fan-shaped expander (Figure 1) was designed for mandible advancement, and the screw was activated once per week. As the original expander reached the limit of expansion after 1 year, we developed a new conventional expander. During the 2-year treatment period, the patient was also treated with CPAP (AirSense 10 AutoSet FH Plus C) (Figure 2).

3 | RESULTS

3.1 | Chief complaint and medical history

The patient was an 8-year-old girl with a chief complaint of narrow arch and crowded dentition. The patient was

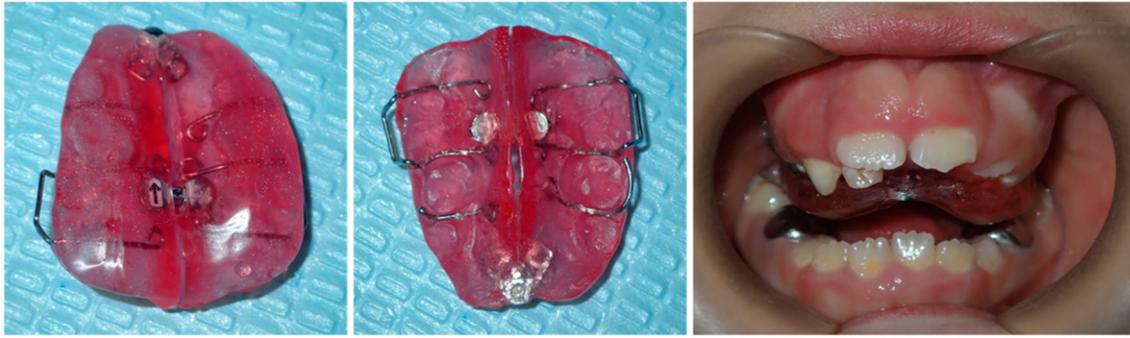


FIGURE 1 Individualized reverse sector fan-shaped expander



FIGURE 2 Patient treated with CPAP

born at full term. She was suspected of having a history of hypoxia at birth, which manifested as bluish nasal ala and low crying capacity. At birth, her weight was 3.2 kg, her body length was 50 cm, and her head circumference was normal. Due to developmental delay and multiple malformations, single-nucleotide polymorphism assay and WES had been performed in another hospital. No variant related to the clinical phenotype was detected. The patient had undergone tonsillectomy, adenoidectomy, and kionorrhaphy. There was no family history.

3.2 | Physical examination

At her first visit to our hospital, the patient's height was 120 cm and her weight was 29 kg. She did not experience hearing loss. She had mild intellectual disability, motor delay, muscle weakness, developmental delay, and characteristic dysmorphic facial features (prominent forehead, thick, high, and arched eyebrows, widely spaced eyes, downslanting palpebral fissures, low-set ears, depressed nasal bridge, and a short and upturned nose) and mouth breathing (Figure 3). She could not walk and stand stably. There were no obvious abnormalities in her liver, kidneys, lungs, and heart. Brain imaging showed that the frontal bone was sharp and the temporal bone was protrusive. There was an arachnoid cyst in the right occipital brain (maximum cross-sectional area, 20×18 mm). The patient's spine was bent to the right. There was a mass shadow on the right side of the thoracic spine below the upper edge of T6, the exterior margin of which was clear.

3.3 | Intraoral examination

The patient presented with mixed dentition. The upper and lower arches were extremely narrow, with severe dental crowding. She had a normal overbite, deep overjet (8 mm), and a class II molar relationship. There were stainless steel crowns on 54, 55, 65, 75, and 85 (Figure 4).

3.4 | Cephalometric analysis and panoramic radiography

Cephalometric analysis showed severe sagittal hypoplasia of the maxilla and mandible (sella-nasion-subspinale: 76.3° , sella-nasion-supramental: 70.2°), mandibular skeletal retrusion (subspinale-nasion-supramental [ANB]: 6.1°), and extremely steep mandibular plane (sella-nasion-gonion-gnathion [SN-GoGn]: 53°). The upper airway was narrow (Figure 5).



FIGURE 3 Facial photographs at first visit



FIGURE 4 Intraoral photographs at first visit



Measurement data	Pre	Standard
SNA (°)	76.3	82.3 ± 3.5
SNB (°)	70.2	77.6 ± 2.9
ANB (°)	6.1	4.7 ± 1.4
Go-Gn to SN (°)	53	35.8 ± 3.6
Saddle angle (°)	131.8	123
U1 to SN (°)	96.96	104.8 ± 5.3
U1 to APog (mm)	7.7	7.7 ± 1.6
L1 to Go-Gn (°)	69.8	94.7 ± 5.2
U1 to L1 (°)	131.4	122 ± 6
Lower lip (mm)	7.6	-2
Upper lip (mm)	6.6	0

FIGURE 5 Lateral cephalogram at first visit

Panoramic radiography showed congenital absence of 15 and 25 (Figure 6).

3.5 | Polysomnography

The apnea/hypopnea index (AHI) was 6.8. The longest time of apnea and hypopnea was 31.5 s and 52.5 s, respectively. The average and minimum oxygen saturation were 98% and 80%, respectively. The patient was diagnosed as having moderate OSA and moderate nocturnal hypoxia.

3.6 | Gene testing

WES revealed a de novo *MN1* variant, c.3760C>T (p.[Q1254*]), located at the extreme 3' region of exon 1 (Figures 7 and 8).



FIGURE 6 Panoramic radiograph at first visit

FIGURE 7 Protein structures of wild-type MN1 and MN1 carrying the de novo variant

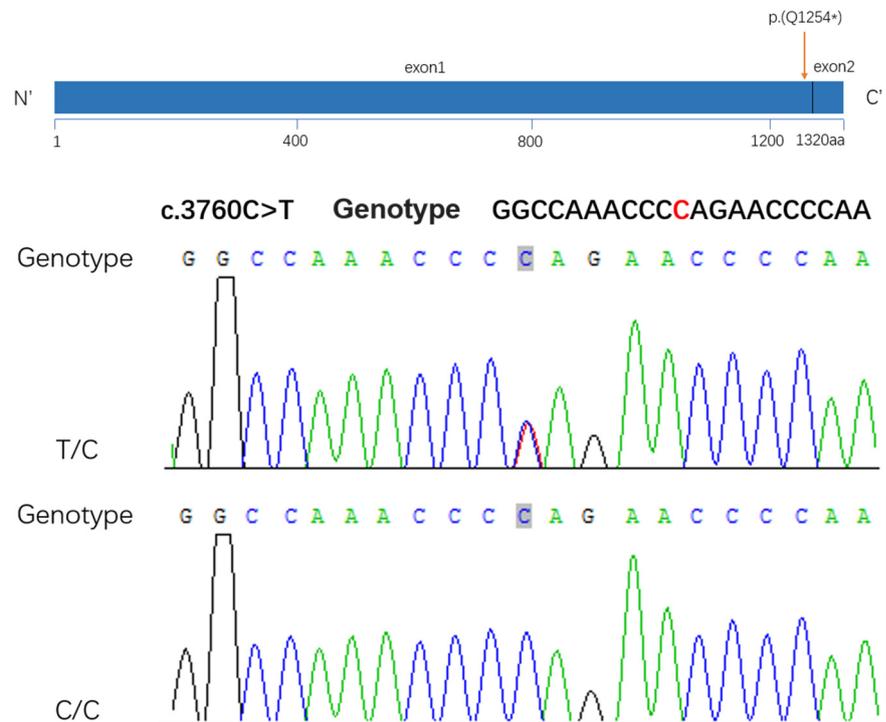


FIGURE 8 Sanger sequencing result of the *MN1* variant

3.7 | Treatment

The patient received combined orthodontic and respiratory treatment. In the Department of Orthodontics, an individualized reverse sector fan-shaped expander was designed for her. Cleft secondary palate could be observed intraorally, along with widening of the upper arch (Figure 9).

After 2 years of treatment, the patient's upper arch was widened, and dental crowding was partially solved. The overjet decreased to 4 mm, the chin moved forward, and the profile became straight (Figure 10). A lateral cephalogram was taken again. At that time, cephalometric analysis showed that the mandible had obviously developed in the sagittal dimension, and the sagittal relationship between the maxillary and mandibular molars was normalized (ANB: 3.8°). The high angle was significantly improved (SN-GoGn: 49.0°). The airway width increased, which significantly improved the quality of life of the patient (Figure 11). Developmental delay, motor delay, and muscle weakness were significantly improved. AHI decreased to approximately 1 after CPAP during the night. Her height was 132 cm and her weight was 38 kg.

4 | DISCUSSION

Our patient presented with mild symptoms of classic MCTT syndrome, including mild intellectual disability, motor delay, muscle weakness, developmental delay, characteristic dysmorphic facial features, class II



FIGURE 9 Intraoral photographs after 2 years of treatment



FIGURE 10 Facial photographs after 2 years of treatment

malocclusion, cleft secondary palate, and moderate OSA (Figure 12). The patient carried a de novo *MNI* mutation, c.3760C>T (p.[Q1254*]), located in the extreme 3' region of exon 1. The variant created a premature stop codon. She received 2 years of multidisciplinary treatment with maxillary expansion and CPAP. Maxillary expansion resulted in spontaneous sagittal development of the mandible, leading to significant improvements in her profile and overjet. The AHI decreased to approximately 1 after nightly CPAP for 2 years. Her general physical condition, including the motor delay, muscle weakness, and developmental delay were also significantly improved, without any other treatment.

Among the patients reported by Mak, Doherty, et al. (2020) and Miyake et al. (2020), the proportion of

intellectual disability was high (19/26), which might be related to different brain abnormalities in these patients. Our patient did not have hearing loss. She had mild intellectual disability and attended a normal school. Her brain MRI showed no abnormalities, except for an arachnoid cyst in the right occipital brain. In addition to our patients, brain MRI of two reported Chinese patients also showed no abnormalities (Tian et al., 2021; Zhao et al., 2021). Therefore, no typical brain MRI as previously reported (Mak, Doherty, et al., 2020) has been found in Chinese patients.

In patients with MCTT syndrome, a high arched palate is common (18/25) (Mak, Doherty, et al., 2020; Miyake et al., 2020; Tian et al., 2021), but only one patient had a submucous cleft palate associated with a bifid uvula



Measurement data	Post	Standard
SNA (°)	78.8	82.3 ± 3.5
SNB (°)	75.2	77.6 ± 2.9
ANB (°)	3.6	4.7 ± 1.4
Go-Gn to SN (°)	49.0	35.8 ± 3.6
Saddle angle (°)	136.6	123
U1 to SN (°)	106.1	104.8 ± 5.3
U1 to APog (mm)	8.8	7.7 ± 1.6
L1 to Go-Gn (°)	78.5	94.7 ± 5.2
U1 to L1 (°)	119.4	122 ± 6
Lower lip (mm)	5.3	-2
Upper lip (mm)	5.7	0

FIGURE 11 Lateral cephalogram after 2 years of treatment

Clinical Features	Incidence	Our Case
Developmental delay	26/27	+
Speech delay	22/24	+
Motor delay	19/20	+
Intellectual disability	16/17	Mild
Hearing loss	17/22	-
OSA	-	Moderate
Brain MRI abnormality	13/16	Normal except an arachnoid cyst in the right occipital brain
High-arched/narrow palate	18/25	+
Cleft palate	2/25	+
Hypotonia	20/23	unknown
Muscle weakness	-	+
Feeding difficulty	15/22	-
Mouth breathing	-	+
Hyperphagia	3/3	+
Cranial anomaly	20/26	Sharp frontal bone and protrusive temporal bone
Characteristic face defects	27/27	+
Midface hypoplasia	21/22	+
Downslanting palpebral fissures	15/21	+
Ear anomalies	26/26	+
Short and upturned nose	25/26	+

FIGURE 12 Clinical features compared with other patients

(Mak, Doherty, et al., 2020) and one had palate cleft (Tian et al., 2021). In our case, the initial diagnosis was also submucous cleft palate. However, after 2 years of maxillary expansion, we found that palatal shelves were separated and changed into a cleft secondary palate. At her first visit, the mucosa of the palatal shelves was confluent because of the narrow upper dental arch, which led to a misdiagnosis of submucous cleft palate. Several patients with a heterozygous deletion involving *MN1* reportedly had orofacial features, including a cleft palate. Meester-Smoor et al. (2005) reported that *Mn1*^{-/-} knockout mice

consistently had cleft secondary palate, while 15% of *Mn*^{+/-} knockout mice had less severe defects and the palatal shelves formed small rugae. Further, the cleft palate was narrow in *Mn1* knockout mice. Studies in mice have shown that *MN1* is also involved in palate development, suggesting that *MN1* should be considered as a candidate gene for cleft palate (Beck et al., 2015; Liu et al., 2008; Meester-Smoor et al., 2005). Some previously reported MCTT syndrome patients may have been misdiagnosed because of a narrow upper arch. Thus, clinicians should pay more attention to cleft palate and further research

should be carried out to elucidate the pathogenesis of cleft secondary palate in MCTT syndrome patients.

This is the first case of MCTT syndrome complicated with OSA. OSA is characterized by partial or complete airway obstruction during sleep, resulting in hypoxemia and hypercapnia. Sleep disorders in children can be associated with cardiovascular problems, impaired growth, and learning and behavioral problems. On the one hand, hypoplasia of the maxillofacial tissues caused by *MN1* mutation may result in narrow upper airway and nocturnal airway insufficiency. On the other hand, *MN1* mutation itself may cause hypoxia and OSA. Some patients with *MN1* deletions presented with Pierre-Robin syndrome (Davidson et al., 2012; Said et al., 2011). Homozygous mice with *Mn1* knockout died of dyspnea after birth without abnormalities in lung function and development (Meester-Smoor et al., 2005). Thus, it is reasonable to assume that OSA was caused directly by the *MN1* mutation, and its mechanism is worthy of further investigation. Hypoxia signature genes reportedly were significantly co-upregulated in mice carrying *Asx1* mutation compared to wild-type mice, in the presence of *MN1* overexpression (Said et al., 2011). If *MN1* mutation did lead to dyspnea, it may also explain the motor delay, muscle weakness, developmental delay, and intellectual disability as well as the improvement of systemic symptoms after treatment with CPAP and maxillary expansion.

The recommended management of MCTT syndrome is to help manage developmental delay/intellectual disability, feeding issues, seizures, hearing loss, and speech and language needs through alternative communication (Mak, Fung, et al., 2020). The curative effect of such treatment has not been reported. We took a multidisciplinary treatment approach for the patient, mainly focusing on her hypoplasia of the upper arch and moderate OSA (Luzzi et al., 2019). As the upper arch of the patient was extremely narrow, we could not find a suitable maxillary expander. Thus, we designed a maxillary expander (Figure 1) especially for the patient, which successfully expanded the upper arch. It provided space for sagittal development of the mandible and as a consequence, increased the upper airway width. The patient's facial profile also improved. The maxillofacial development, developmental delay, motor delay, and muscle weakness significantly improved without any other treatment. As the patient could not stand stably at her first visit, radiographs were taken with the help of her mother. Her mother's fingers can be seen in the lateral cephalograph and panoramic radiographs (Figures 5 and 6). After approximately 2 years of treatment, the patient could stably stand by herself and the second lateral cephalogram was taken without help (Figure 11). It is reasonable to speculate that the upper airway widening through maxillary expansion and relieve of sleep apnea through CPAP treatment improved her

general physical condition. If this is true, orthodontic and respiratory multidisciplinary treatment should be considered as a main treatment for MTCC syndrome.

5 | CONCLUSION

We identified a novel *MN1* variant [NM_002430.2: c.3760C>T, p.Q1254*] that causes mild symptoms as compared to other *MN1* variants. For patients with MCTT complicated with OSA, multidisciplinary combination therapy can widen the upper airway and relieve sleep apnea, improving the general physical condition.

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CONFLICT OF INTEREST

Jingjia Yu and Chen Li contributed equally to this study.

AUTHOR CONTRIBUTIONS

Jingjia Yu: Writing - original draft, visualization, data curation. Chen Li: Data curation, investigation, formal analysis. Jialin Chen: Data curation. Qiuchi Ran: Data curation. Yingya Zhao: Data curation. Qingxin Cao: Formal analysis. Ximeng Chen: Formal analysis. Linnan Yu: Formal analysis. Wenyang Li: Respiratory therapy, data curation. Zhenjin Zhao: Writing - review & editing, orthodontic treatment, supervision.

ETHICAL APPROVAL

This study was approved by the ethics committee of China Medical University, Hospital of Stomatology (approval No.: 2021–20).

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