Distinctive Craniofacial and Oral Anomalies in MN1 C-terminal Truncation Syndrome

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MN1 C-terminal truncation (MCTT) syndrome was first reported in 2020 and only 28 patients have been recorded to date. Since MCTT syndrome is a newly defined and rare syndrome with many clinical features, the present study reviewed the manifestations and management of oral and dental anomalies. Gene variants of MCTT syndrome and their positive phenotypes were summarised. The phenotypes of variants in two exons differed from each other mainly in the craniofacial region, including brain MRI abnormalities and palatal morphology. Pathogenic mechanisms, especially in craniofacial and oral anomalies, were discussed. Appropriate treatments in the stomatology and respiratory departments could improve the symptoms of MCTT syndrome. The different sites of MN1 gene variants may influence the clinical symptoms and there may be racial differences in MCTT syndrome. We recommend oral and pulmonary evaluations for the multidisciplinary treatment of MCTT syndrome.

Keywords: craniofacial and oral anomalies, MN1 C-terminal truncation syndrome, MN1 gene variant.


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ventricular septal defects, seizures, hyperphagia, cleft palate and congenital diaphragmatic hernia.¹,³

*MNI* gene variants lead to MCTT syndrome. *MNI*, located at chromosome 22q12.1, is a transcriptional coregulator composed of two exons and that encodes 1,320 amino acid residues. The t (4;22) gene variant was first reported in meningioma and t (12;22) in myeloproliferative diseases.⁷,⁸ *MNI* is closely related to haematological malignant tumours, especially acute myeloid leukaemia, and high expression of *MNI* is related to poor prognosis.⁹-¹¹

Variants in *MNI* at different sites lead to different clinical symptoms. MCTT syndrome is a variant in *MNI* located at the terminal exon or extreme 3' region of exon 1. To date, 16 different variant sites have been identified in MCTT syndrome (Fig 1 and Table 1), resulting in different clinical symptoms (Table 1).¹,³-⁶ Among the 16 variant sites, six variant sites of six patients were located in the extreme 3' region of exon 1, including all three reported Chinese patients.¹,⁴,⁶ Ten variant sites of 22 patients were located at exon 2. For patients with variants in exon 1, symptoms with an incidence of more than 90% included developmental delay, speech delay, motor delay, intellectual disability, characteristic facial defects, ear anomalies and hypertelorism, which were consistent with those of patients with variants in exon 2 (Table 1). The phenotypes of variants in the two exons differed from each other mainly in the cranio-maxillofacial region. The incidences of brain magnetic resonance imaging (MRI) abnormalities and palatal morphology differed between the two groups.

The incidence of brain MRI abnormalities in exon 2 was 82%, which was 32% higher than that in exon 1. Notably, none of the three Chinese patients had symptoms of brain MRI abnormalities.

All patients with MCTT syndrome showed characteristic facial features, and 93% of patients had maxillary hypoplasia. Consequently, a high-arched palate was commonly observed (Table 1).¹,³-⁵ In terms of palatal morphology, the incidence of a high-arched/narrow palate in exon 2 was 76% and 50% in exon 1. Among all the reported patients with MCTT syndrome, only three were diagnosed with cleft palate. Two of these were Chinese, and all three variant sites were located in the extreme 3' region of exon 1 and the incidence was 50%. One patient was diagnosed with a submucosal cleft palate with bifid uvula.¹ One Chinese patient was diagnosed with cleft palate.¹ The initial diagnosis of another Chinese patient was submucosal cleft palate,⁵ consistent with the previous case reported;¹ however maxillary expansion was performed over 2 years and widened the maxilla, and the cleft secondary palate became visible, possibly because the maxillary hypoplasia and narrow maxilla resulted in the maxilla and palate adhering to each other.⁵ The incidence of cleft palate associated with MCTT syndrome may be related to race or variant location. Although these are uncertain at present due to the small number of reported cases, whether cleft palate should be included as a common symptom of MCTT syndrome merits further research.

Narrowing of the maxilla could influence mandibular development, resulting in reactive mandibular protrusion or retrusion. The clinical symptoms of mandible positions varied in the reported cases, including eight cases of normal mandibular development, six of mandibular protrusion and five of mandibular hypoplasia. These indicated that the development of the maxilla was affected, whereas that of the mandible was normal in MCTT syndrome.¹

In addition, one patient had obstructive sleep apnoea (OSA) syndrome. Maxillary hypoplasia and mandibular retrusion are significant causes of a narrow upper airway in patients with OSA.⁵,¹² Hypoxemia and hypercapnia are caused by frequent apnoea and hypopnea in children with OSA. OSA causes damage to various systems, resulting in several complications such as poor memory, impaired growth, learning and behavioural problems, and other cognitive impairments. Children with severe or untreated OSA also suffer from serious cardiovascular complications.¹³,¹⁴ It aggravates other symptoms such as muscle weakness and developmental delay in patients with MCTT syndrome, which requires immediate attention.

**Possible pathogenic mechanisms**

In MCTT syndrome, gene variants lead to C-terminally truncated protein expression. Our unpublished results showed that the mutant MN1 protein (c. 3760C > T, p. Q1254 *) leads to the deletion of a terminal helix structure due to the premature stop codon (Fig 2).

Both wild-type and mutant-type MN1 proteins were localised in the nucleus.³,⁴ Mutant MN1 proteins tended to aggregate more than wild-type MN1 proteins, possibly due to the increased number of intrinsically disordered regions in MN1 proteins that cause phase separation; however, the specific pathogenic mechanisms underlying MCTT syndrome remain unclear.

Miyake et al³ confirmed that the MN1 variant led to escape nonsense-mediated mRNA decay and the MN1 protein was degraded by the ubiquitin-proteasome pathway. Mutant MN1 proteins showed higher stability than the wild-type. The C-terminal region of MN1 is degraded by the ubiquitin-proteasome pathway. MN1
participates in the transcriptional regulation of target genes by interacting with transcription factors Pre-B-Cell Leukaemia Homeobox 1 (PBX1), PBX/Knotted Homeobox 1 (PKNOX1) and Zinc Finger Protein 450 (ZBTB24). The binding of mutant MN1 to E3 ubiquitin ligase ZBTB24 and Really Interesting New Gene 1 (RING1) protein is impaired, which interferes with the degradation of MN1 protein resulting in mutant MN1 protein aggregation and imbalanced MN1-related transcription.3

All patients with MCTT syndrome exhibited midfacial hypoplasia, but the underlying mechanism by which MN1 affects midfacial development remains unclear. MN1 plays an important role in maintaining the proliferation, differentiation and function of osteoblasts, and is related to craniofacial development.

Table 1 The incidence of different clinical symptoms in the reported MCTT syndrome patients.

<table>
<thead>
<tr>
<th>Clinical symptoms*</th>
<th>All patients (positive/total) and positive/total %</th>
<th>Patients with different variant sites of mutant-MN1 Exon 1 (positive/total) and positive/total %</th>
<th>Exon 2 (positive/total) and positive/total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental delay</td>
<td>(27/27) 100%</td>
<td>(5/5) 100%</td>
<td>(22/22) 100%</td>
</tr>
<tr>
<td>Speech delay</td>
<td>(24/26) 92%</td>
<td>(5/5) 100%</td>
<td>(19/21) 90%</td>
</tr>
<tr>
<td>Motor delay</td>
<td>(24/25) 96%</td>
<td>(4/4) 100%</td>
<td>(20/21) 95%</td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>(17/18) 94%</td>
<td>(3/3) 100%</td>
<td>(14/15) 93%</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>(18/26) 69%</td>
<td>(4/6) 67%</td>
<td>(14/20) 70%</td>
</tr>
<tr>
<td>OSA</td>
<td>(1/1) 100%</td>
<td>(1/1) 100%</td>
<td>NR</td>
</tr>
<tr>
<td>Brain MRI abnormalities</td>
<td>(17/23) 74%</td>
<td>(3/6) 50%</td>
<td>(14/17) 82%</td>
</tr>
<tr>
<td>High-arched/narrow palate</td>
<td>(19/27) 70%</td>
<td>(3/6) 50%</td>
<td>(16/21) 76%</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>(3/27) 11%</td>
<td>(3/6) 50%</td>
<td>(0/21) 0%</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>(20/23) 87%</td>
<td>(4/5) 80%</td>
<td>(16/18) 89%</td>
</tr>
<tr>
<td>Feeding difficulty</td>
<td>(15/24) 63%</td>
<td>(3/5) 60%</td>
<td>(12/19) 63%</td>
</tr>
<tr>
<td>Cranial anomaly</td>
<td>(21/27) 78%</td>
<td>(5/6) 83%</td>
<td>(16/21) 76%</td>
</tr>
<tr>
<td>Characteristic facial defects</td>
<td>(28/28) 100%</td>
<td>(6/6) 100%</td>
<td>(22/22) 100%</td>
</tr>
<tr>
<td>Midface hypoplasia</td>
<td>(25/27) 93%</td>
<td>(4/5) 80%</td>
<td>(21/22) 95%</td>
</tr>
<tr>
<td>Mandibular skeletal retrusion</td>
<td>(6/22) 27%</td>
<td>(1/4) 25%</td>
<td>(5/18) 28%</td>
</tr>
<tr>
<td>Down slanting palpebral fissures</td>
<td>(16/22) 72%</td>
<td>(3/4) 75%</td>
<td>(13/18) 72%</td>
</tr>
<tr>
<td>Ear anomalies</td>
<td>(28/28) 100%</td>
<td>(6/6) 100%</td>
<td>(22/22) 100%</td>
</tr>
<tr>
<td>Short and upturned nose</td>
<td>(26/28) 93%</td>
<td>(5/6) 83%</td>
<td>(21/22) 95%</td>
</tr>
<tr>
<td>Hypertelorism</td>
<td>(24/26) 92%</td>
<td>(5/5) 100%</td>
<td>(19/22) 90%</td>
</tr>
</tbody>
</table>

NR, not reported.

*Not all case reports mention all the clinical symptoms, so the “total” number may not be 28.
in mice and humans.\textsuperscript{15-17} In vitro experiments showed that \textit{MNI} plays a key role in regulating osteoblast proliferation.\textsuperscript{16} Moreover, \textit{MNI} is important for intramembranous bone formation. Evolutionary analysis has shown that \textit{MNI} appears at the base of bony vertebrates, where the ossified head emerges.\textsuperscript{15} Thus, \textit{MNI} is a key gene involved in skull formation and variations in skull shapes within a population.\textsuperscript{15} \textit{MNI} plays an important role in maintaining the normal maturation and function of skull osteoblasts, and is related to brain and craniofacial development in mice and humans.\textsuperscript{17}

Half of the patients with variants in exon 1 were reported to have cleft palate but the underlying mechanism was unclear. The deletion of \textit{MNI} affects the development of membranous bone in mice, with some symptoms resembling the human phenotype, such as craniofacial abnormalities (mandibular retrusion is common), cleft palate, speech delay, feeding problems, vestibular schwannomas and corpus callosum agenesis.\textsuperscript{18-22} \textit{MNI} is involved in the development of cleft palate in mice.\textsuperscript{23,24} Meester-Smoor et al\textsuperscript{24} constructed an \textit{MNI} knockout transgenic mouse model and found that \textit{MNI} homozygous knockout mice usually died at birth due to secondary cleft palate, whereas 15\% of \textit{MNI} heterozygous knockout mice had mild palate defects and formed a narrow cleft palate. It has been suggested that \textit{MNI} should be considered a candidate gene for cleft palate, prompting us to further investigate the effect of \textit{MNI} gene variants on craniofacial development, especially on cleft palate.

One case of MCTT syndrome was complicated by OSA.\textsuperscript{5} Among the reported cases, patients with MCTT syndrome had developmental delays and hypotonia. Miyake et al\textsuperscript{3} found that \textit{MNI} is highly expressed in foetal and adult skeletal muscle. Some patients with \textit{MNI} deletions have Pierre-Robin syndrome.\textsuperscript{21,22} Homozygous \textit{MNI} knockout mice died of dyspnoea after birth, with no pulmonary function or developmental abnormalities.\textsuperscript{24} In the case of \textit{MNI} overexpression, hypoxia-related genes were significantly upregulated in mice carrying Additional Sex Combs-Like Transcriptional Regulator 1 (\textit{ASXL1}) variants compared with those in wild-type mice.\textsuperscript{25} OSA causes hypoxia, which usually inhibits osteoblast activation and proliferation.\textsuperscript{26} Utting et al\textsuperscript{27} noted that exposure to hypoxia delays osteoblast growth and differentiation, and decreases bone formation. In addition to decreased osteoblast production, osteoblast matrix mineralisation is inhibited during hypoxia due to the decreased expression and activity of alkaline phosphatase.\textsuperscript{26,28} Hypoxia stabilises an increase in the number and activity of osteoclasts;\textsuperscript{29} however, persistent hypoxia can inhibit osteoclast formation and activity due to extensive cell death.\textsuperscript{30} Thus, the relationship between OSA and \textit{MNI} variants and the underlying mechanisms warrant further investigation.

**Treatment**

Currently, there are no reports on treatment results and the efficacy of treatment in patients with MCTT syndrome. It is advisable to treat the patient’s clinical symptoms with rehabilitation, speech training and cardiovascular therapy.\textsuperscript{2} Multidisciplinary experts can address
problems such as developmental delays, intellectual disabilities, feeding problems, epilepsy, hearing loss and speech delay, and refer patients to stomatologists for treatment only if there is a malocclusion. Only one study reported the effect of treatment in the orthodontic and respiratory department settings (Fig 3). Using a reverse sector fan-shaped expander, the patient’s maxilla was widened to provide space for the development of the mandible, and continuous positive airway pressure was used during this period to improve the patient’s respiratory condition. After 2 years of treatment, the OSA and the patient’s condition improved, and systemic problems such as developmental delays and muscle weakness were also improved significantly, suggesting that despite the abnormal maxillary development in this patient, the mandibular development conformed to the natural course of growth and development. Therefore, the author recommended oral and pulmonary evaluations for multidisciplinary treatment of MCTT syndrome. For patients with narrow maxillae, the author recommended expanding the arches to enlarge the oral volume in those with the potential for growth and development; however, once the narrowing of the upper airway and hypoxia are observed, it is necessary to conduct appropriate examination and treatment in the respiratory department. At present, there is only one report on therapeutic effect. Thus, it is necessary to conduct further investigation and verification.

Summary

The different sites of gene variants may influence the clinical symptoms of MCTT syndrome and there may be racial differences. Characteristic features such as dysplasia of the palate and developmental delay suggest the possibility of MCTT syndrome, which can be diagnosed by whole genome sequencing. The craniofacial anomalies and developmental delays attributed to this syndrome would benefit from optimising care with a particular focus on the teeth, palate, maxilla and upper airway. We also recommend oral and pulmonary evaluations for multidisciplinary treatment of MCTT syndrome. Further studies on the clinical characteristics and pathogenic mechanisms may help develop long-term treatment strategies and establish a multidisciplinary treatment system to improve the quality of life of patients with MCTT syndrome.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Dr Jing Jia YU designed the research and drafted the manuscript; Dr Qiuyi WU revised the manuscript; Drs Qiu Chi RAN and Ying Ya ZHAO made the figures; Drs Lin Nan YU, Qing Xin CAO and Xi Meng CHEN collected data and made tables; Professor Wen Yang LI revised the manuscript; Professor Zhen Jin ZHAO supervised the study and revised the manuscript.

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