Combined MECP2 duplication syndrome and ADNP syndrome in a Chinese boy: a case report and literature review

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Case Report

Keywords: MECP2 duplication syndrome, ADNP syndrome, Recurrent respiratory infections, Growth retardation, China

Posted Date: July 31st, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3148449/v1

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Abstract

**Background** Methyl-CpG-binding protein 2 (MECP2) acts as a transcriptional repressor or activator regulating the genes associated with nerve system development. The increased copy number of MECP2 can cause a new X-linked intellectual disability syndrome named MECP2 duplication syndrome (MDS), which is characterized by a broad range of neurodevelopmental abnormalities, as well as hypotonia, recurrent respiratory infections, and facial dysmorphism. ADNP syndrome is caused by heterozygous de novo mutations in the Activity Dependent Neuroprotective Protein (ADNP) gene, which is characterized by global developmental delay, intellectual disability, language impairment, autism spectrum, and variable extraneurologic features. We reported here the first infant case combined MDS and ADNP syndrome.

**Case presentation** A 6-month boy was hospitalized with a complaint of cough and fever for 7 days. He was born at 40 weeks of gestation with intrauterine growth retardation. He had pneumonia twice since birth, at 1-month and 4-month, respectively. He showed obviously weight and height growth retardation since birth. His motor developmental milestone was obviously delayed. Physical examination revealed no obviously abnormal dysmorphic features. Except for hypotonia, no other neurodevelopmental or ophthalmologic deficits were observed. Genetic analysis revealed that the boy carried a chromosome g.151283637_154348425dup, this area contains Xq28 region (includes MECP2). The boy also carried a de novo ADNP variant heterozygously, c.2194_2197del (p.Leu732MetfsTer20), in exon 5. He fulfilled the diagnostic criteria of MDS and ADNP syndrome.

**Conclusion** We identified a de novo X chromosome g.151283637_154348425dup and a de novo c.2194_2197del (p.Leu732MetfsTer20) in ADNP gene, in a 6-month boy with clinical features of recurrent respiratory infections, growth retardation and hypotonia in China. We reported here the first infant case combined MDS and ADNP syndrome.

**Background**

Methyl-CpG-binding protein 2 (MECP2) located at Xq28 acts as a transcriptional repressor or activator regulating the genes associated with nerve system development(1). The loss of MECP2 is associated with Rett syndrome in females and a wide variety of phenotypes including nonspecific intellectual disability in males, while the increased copy number of MECP2 can cause a new X-linked intellectual disability syndrome named MECP2 duplication syndrome (MDS; OMIM 300260)(2, 3). As a rare and severe genomic imbalance disorder, MDS is characterized by a broad range of neurodevelopmental abnormalities (severe intellectual disability, developmental delay, seizure, speech delay/deficit, autism spectrum disorder), as well as hypotonia, recurrent respiratory infections, and facial dysmorphism. Moreover, the phenotypic spectrum of this syndrome is expanding constantly(4, 5).

ADNP syndrome, also called Helsmoortel–van der Aa syndrome (HVDAS), is caused by heterozygous de novo mutations in the Activity Dependent Neuroprotective Protein (ADNP) gene. ADNP syndrome is
characterized by global developmental delay, intellectual disability, language impairment, autism spectrum, and variable extraneurologic features\(^6\), \(^7\).

Here we report firstly a Chinese boy combined MDS and ADNP syndrome, who presented with recurrent respiratory infections, growth retardation and hypotonia.

**Case presentation**

A 6-month boy was hospitalized with a complaint of cough and fever for 7 days. The proband was born to non-consanguineous healthy parents. He was born at 40 weeks of gestation with a birth weight of 2.5 kg \((< P_{3\text{th}})\), a length of 46 cm \((< P_{3\text{th}})\), and a head circumference of 32 cm \((< P_{3\text{th}})\). He had pneumonia twice since birth, at 1-month and 4-month, respectively. He had a 2-year-old healthy sister. He showed obviously weight and height growth retardation since birth, see Fig. 1. His motor developmental milestone was obviously delayed. He began to rise head at 5 months but could not hold head steadily.

He had no history of chronic diarrhea, vomiting, feeding improper or difficulty. He had also no signs of seizure. There was no family history of tuberculosis and nutritional diseases.

At admission at 6 months of age, his weight was 6 kg \((< P_{3\text{th}})\), height was 62 cm \((< P_{3\text{th}})\), and head circumference was 38 cm \((< P_{3\text{th}})\). He could make sounds, look and hear with audiovisual stimulations. He could not turn over and sit. Physical examination revealed no obviously abnormal dysmorphic features. His breath was fast, 50 times per minute, bubble sounds could be heard in both lungs. There were no abnormalities in the examination of his heart and abdomen. Except for hypotonia, no other neurodevelopmental or ophthalmologic deficits were observed.

The routine laboratory tests were all normal, including thyroid hormone, growth hormone, insulin-like growth factor 1, the routine blood and urine test, liver, renal function and T/B lymphocyte subsets, see Table 1. The levels of C3 and C4 were below while varieties autoantibodies including antinuclear antibody, anti-double stranded DNA antibodies, extractable nuclear antibodies and anti-neutrophil cytoplasmic antibodies were all negative. Blood metabolism analysis and urine metabolism analysis were all normal. Gesell development schedules showed that the estimated value of total DQ was 52, adaptive behavior DQ was 58, large motor behavior DQ was 45, fine motor behavior DQ was 46, language behavior DQ was 55, and personal social behavior DQ was 56, respectively. Echocardiography showed patent foramen oval (2.4mm). Electroencephalogram examination was normal. His cranial magnetic resonance imaging (MRI) showed no abnormal findings. His karyotype analysis was 46, XY.
### Table 1
Laboratory examinations of the boy

<table>
<thead>
<tr>
<th>Items</th>
<th>Results</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total serum protein</td>
<td>66.0 g/L</td>
<td>65–84</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>40.0 g/L</td>
<td>39–54</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>86.0 g/L</td>
<td>120–155</td>
</tr>
<tr>
<td>IgG</td>
<td>8.24 g/L</td>
<td>7–16</td>
</tr>
<tr>
<td>IgA</td>
<td>0.80 g/L</td>
<td>0.7–5</td>
</tr>
<tr>
<td>IgM</td>
<td>0.75 g/L</td>
<td>0.4–2.8</td>
</tr>
<tr>
<td>C₃</td>
<td>0.73 g/L</td>
<td>0.78–2.1</td>
</tr>
<tr>
<td>C₄</td>
<td>0.07 g/L</td>
<td>0.17–0.48</td>
</tr>
<tr>
<td>Total parathyroid hormone</td>
<td>82.6 ng/L</td>
<td>50–330</td>
</tr>
<tr>
<td>25-OH vitamin D</td>
<td>30.8 µg/L</td>
<td>30–100</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>4.7 µg/L</td>
<td>0.034–9.012</td>
</tr>
<tr>
<td>Insulin-like growth factor-1</td>
<td>123.5 µg/L</td>
<td>57–312</td>
</tr>
<tr>
<td>Insulin</td>
<td>7.2 mIU/L</td>
<td>2.2–25</td>
</tr>
<tr>
<td>Thyroid stimulating hormone</td>
<td>0.8 mIU/L</td>
<td>0.51–4.94</td>
</tr>
<tr>
<td>Tetraiodothyronine</td>
<td>78.6 µg/L</td>
<td>32–126</td>
</tr>
<tr>
<td>Triiodothyronine</td>
<td>1.2 µg/L</td>
<td>0.6–1.81</td>
</tr>
<tr>
<td>Free Tetraiodothyronine</td>
<td>13.0 ng/L</td>
<td>8.9–17.6</td>
</tr>
<tr>
<td>Free Triiodothyronine</td>
<td>3.2 ng/L</td>
<td>2.3–4.2</td>
</tr>
</tbody>
</table>

Because the boy presented with recurrent respiratory infections (three times pneumonia), growth retardation, hypomyotonia and low DQ of Gesell development schedules, genetic neurodevelopmental disorders were considered. Genetic analysis was performed using whole exons sequencing in the genetics laboratories of MyGenostics biotechnology companies in China. Results revealed that the boy carried a chromosome g.151283637_154348425dup, his mother and father were both normal, see Fig. 2. This area contains Xq28 region (includes MECP2), Xq28 recurrent region (includes GDI1), includes 79 genes (PLXNB3, OPN1LW, AVPR2, LAGE3, ATP6AP1, PNMA3, SLC6A8, GABRQ, BCAP31, TKTL1, ZNF275, PNMA6F, CSAG3, CETN2, SMIM9, RPL10, SLC10A3, MAGEA3, GABRA3, BGN, MAGEA5, MAGEA6, FAM3A, PLXNA3, MTCP1, HCFC1, ATP2B3, TEX28, ZNF185, RENBP, PNMA6A, FLNA, DKC1, TAZ, PDZD4, CTAG2, IKBKG, MAGEA12, MAGEA10, OPN1MW2, PNMA5, G6PD, NAA10, BRCC3, ARHGAP4, GAB3, CMC4, UBL4A, PNCK, PNMA6E, F8, MECP2, FUNDCL2, SRPK3, SSR4, MAGEA2B, MAGEA2, CTAG1B, GDI1, FAM50A,
TREX2, EMD, IRAK1, ABCD1, CTAG1A, OPN1MW3, MPP1, NSDHL, IDH3G, DUSP9, CCNQ, TMEM187, MAGEA1, OPN1MW, DNASE1L1, ZFP92, CSAG1, L1CAM, HAUS7).

The boy also carried a de novo ADNP variant heterozygously, c.2194_2197del (p.Leu732MetfsTer20), in exon 5, see Fig. 3. The variant c.2194_2197del was found in the Human Gene Mutation Database (HGMD) (rs1555809984)(8), but not the SNP databases including ALFA, ExAC, GnomAD and TOPMED. PolyPhen-2, SIFT, Variant Taster and GERP++ analysis showed that the variants was pathogenic (ACMG guideline: PVS1 + PS4 + PM2_Supporting + PS2).

Discussion and conclusion

Chromosomal duplication at the Xq28 region including the MECP2 gene, share consistent clinical phenotypes known as MECP2 duplication syndrome (MDS)(9). The typical clinical features include infantile hypotonia, recurrent infections, developmental delay, intellectual disability, dysmorphic features, a broad range of neurodevelopmental disorders as well as a variety of other comorbidities(4, 5, 10). However, the clinical understanding of MDS has been limited both by its rarity and the short history of its recognition as a distinct disorder.

We reported a 6-month Chinese boy presented with recurrent pneumonia and growth retardation from birth to 6-month age. Physical examination revealed hypotonia. Genetic analysis revealed that the boy carried a de novo X chromosome g.151283637_154348425dup. He fulfilled the diagnostic criteria of MDS.

MDS are also reported previously in China. In 2012, Xu(11) reported firstly a Chinese MDS family with two brothers both presented with intellectual disability, autism, lack of speech, slight hypotonia, unsteadiness of movement and slight dysmorphic features. In 2015, Zhang(12) identified a Chinese family with three persons carry MECP2 gene duplication containing 510 Kb (153,113,885 – 153,624,154) and including 16 other genes except MECP2. Only the proband, 2-year-4-month-old boy, showed most symptoms of MECP2 duplication syndrome, while his mother and maternal grandmother were asymptomatic. In 2017, Li(13) reported a Chinese MDS family includes six patients (five males and one female), and four asymptomatic female carriers. The affected male subjects presented with a broad range of neurodevelopmental symptoms (severe intellectual disability, developmental delay, seizure, language deficit, and autism spectrum disorder) as well as facial dysmorphism and other symptoms.

Recurrent respiratory infections is a major early manifestation of MDS and a main death causes of MDS(9). Our MDS case suffered from recurrent pneumonia, three times within 6 months of age. This is similar to the result of other researches. In the study of Ta(9), respiratory infections such as pneumonia, bronchitis and bronchiolitis have been reported in almost three-quarters (367/498) of individuals from 60 studies. Life expectancy in MDS is sparse. of 86 male patients with an intrachromosomal MDS, 27% (23/86) within the French series had died before 25-years of age in contrast to 39% (34/88) in the literature in an earlier review(9). Lim(14) reported 56 cases (49 males and 7 females) with MDS, over half (55%) had been hospitalised for respiratory infections in the first two years of life. Miguet(15) reported the
majority of MDS patients (49/55, 89%) had recurrent and severe respiratory infections requiring numerous hospitalisations, and recurrent ENT (pharyngitis, otitis, sinusitis) and urinary tract infections. In the report of Zhang(12), the 2-year-4-month-old boy showed recurrent respiratory tract infections, and hospitalized for severe pneumonia for several times. In the report of Li(13), 80% male MDS cases (4/5) had recurrent respiratory infection, one died at 16 years while another died at 14 years and 8 months. Tang(16) reported three brothers of unrelated parents with MDS, both had recurrent severe respiratory tract infections from early childhood. The exact mechanisms of recurrent respiratory infections occured with MDS remain unclear. Beside infections secondary to hypoimmunoglobulinemia, aspiration pneumonia due to poor growth is also an important factor, sometimes artificial ventilation therapy is required(17). However, there was no hypoimmunoglobulinemia in our case.

Growth retardation including foetal growth restriction is another major early manifestation of MDS(18). Our case showed both foetal growth restriction and growth retardation after birth. Developmental/psychomotor delay has been reported in most (324/343) individuals from 56 studies(9), which also has been reported in all Chinese MDS cases (11–13).

Moreover, our proband also carried heterozygously a de novo ADNP variant, c.2194_2197del (p.Leu732MetfsTer20), in exon 5. It is well known that the ADNP gene is among the most common heterozygous genetic variants associated with ADNP syndrome, which is a condition that causes developmental delay, hypotonia, intellectual disability, language impairment, autism spectrum disorders, and variable extraneurologic features. The ADNP gene is located on chromosome 20q13. Most of the genetic causes of ADNP syndrome have been reported are as de novo nonsense or frameshift stop variants in exon 5 of ADNP gene(6, 7). The variant of our proband is also a de novo heterozygous frameshift stop variants in exon 5 of ADNP gene, which has been reported previously in ADNP syndrome(8), so our boy also fulfilled the diagnostic criteria of ADNP syndrome. We suggested that the recurrent pneumonia, growth retardation and hypotonia of our boy might be major associated with MDS, while ADNP syndrome might have some effects on growth retardation and hypotonia. Long term follow-up is needed to verify if the boy has other clinical features of ADNP syndrome, such as intellectual disability, language impairment, autism spectrum disorders.

In conclusion, we reported here the first infant case combined MDS and ADNP syndrome. We emphasized that recurrent respiratory infections and growth retardation are the major early manifestation of MDS, genomic structure rearrangement, especially MECP2 duplication should be tested in the patients with the above symptoms as well as other family members, to make an accurate diagnosis and provide a right genetic counseling.

**Declarations**

**Acknowledgements** Not applicable.

**Author contributions** Yun-Xiu Fan contributed to the evaluation and management of the patient, Wu Yang wrote the first draft. Hong-Wen Zhang reviewed and revised the final draft.
Funding  No funding was received for this study.

Data availability  All data generated or analyzed during this study are included in this published article.

Competing interests  The authors declare no competing interests.

Consent for publication  Written informed consent for the publication of clinical details and/or clinical images was obtained from the guardians of the patient. A copy of the consent form is available for review by the editor of this journal.

Ethics approval and consent to participate  Not applicable

References


Figures
Figure 1

Growth curve of the proband. The boy showed obviously growth retardation since birth, his weight, height and head circumference were all below the $P_{3}$ th.
Figure 2

Genetic analysis of the X chromosome. Results showed that the proband carried a de novo X chromosome g.151283637_154348425dup.
Figure 3

Genetic analysis of the ADNP gene. Results showed that the proband carried heterozygously a de novo ADNP variant, c.911_913del (p.S304del), in exon 5.