Case report

Concurrent combined methylmalonic acidemia and homocystinuria with down syndrome in a Chinese preschool Child: An in-depth case report and literature review

Rui Dong [a,b], Chen Liu [b,c], Yulin Liu [b,d], Haiyan Zhang [a,b], Guohua Liu [b,e,*], Yi Liu [a,b,**], Zhongtao Gai [a,b]

[a] Pediatric Research Institute, Children's Hospital Affiliated to Shandong University (Jinan Children's Hospital), Jinan, China
[b] Shandong Provincial Clinical Research Center for Children's Health and Disease, Jinan, China
[c] Neonatology department, Children's Hospital Affiliated to Shandong University (Jinan Children's Hospital), Jinan, China
[d] Department of neuroelectrophysiology, Children's Hospital Affiliated to Shandong University (Jinan Children's Hospital), Jinan, China
[e] Department of Pediatrics, Children's Hospital Affiliated to Shandong University (Jinan Children's Hospital, Jinan), Jinan, China

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ABSTRACT

Background: Dual occurrence of distinct genetic diseases is exceptionally rare, complicating both diagnosis and management when the conditions share overlapping symptoms.

Case presentation: We describe a preschooler girl diagnosed with Down syndrome at 27 months who developed unexplained motor regression with age. Extensive investigations were carried out to elucidate the etiology, encompassing comprehensive neuromuscular and skeletal assessments, radiographic evaluations of the joints, electrophysiological studies, cerebral-spinal magnetic resonance imaging (MRI), hematological biochemical assays, plasma ammonia and lactate levels, full blood count analyses, echocardiography, and chromatography-mass spectrometry-based testing of amino acids, fatty acids, and organic acid metabolites in both blood and urine. Notably, significantly elevated levels of homocysteine and propionylcarnitine were detected in her blood, while urinary methylmalonic acid was also found to be abnormally high. Trio-whole exome sequencing confirmed the diagnosis as Combined methylmalonic acidemia and homocystinuria (Combined MMA and HCU), specifically due to a cblC defect, resulting from two compound heterozygous pathogenic mutations (c.217C > T and c.482G > A) in the *MMACHC* gene. Upon a two-month course of treatment with hydroxocobalamin and ʟ-carnitine, the patient demonstrated moderate improvement in her motor abilities.

Conclusion: Our study highlights the special and intriguing aspects of managing Combined MMA and HCU, emphasizing the value of a comprehensive diagnostic approach that integrates clinical acumen, metabolic screening, and sophisticated molecular analyses for achieving precise diagnoses in such intricate cases.

1. Introduction

Genetic disorders collectively affect an estimated prevalence between 40 and 82 occurrences per 1000 live births [1], with Down syndrome (DS) being a notably prevalent among these, contributing to global statistics of approximately 1 case in every 800 newborns [2]. This chromosomal anomaly presents with a constellation of diverse clinical manifestations, encompassing broad-spectrum developmental delays and distinct craniofacial characteristics, further complicated by a range of multi-systemic issues such as cognitive impairment, hypotonia, sleep disturbances, weakened masticatory muscles (MMH), and pelvic malformations, among others. Phenotypic variability is substantial in DS individuals; intellectual disabilities span from profound limitations to mild cognitive dysfunction, with additional influencing factors including temperament, maternal education, concurrent health issues, and educational environment [3]. Despite extensive study, the precise age-dependent progression and modifiers of functional capacity in DS individuals remain elusive. Due to the frequent occurrence of DS, pediatric healthcare providers are adept at identifying it and commonly rely on standard chromosome karyotyping during preliminary assessments to establish a definitive diagnosis. However, the multifaceted nature of developmental anomalies and the potential for regression in DS patients pose considerable challenges to caregiving, inadvertently elevating the risk that more subtle manifestations of co-existing rare genetic disorders could go undetected—particularly when such disorders exhibit overlapping symptoms or have a delayed onset [4].

Advancements in high-throughput sequencing technologies have dramatically enhanced the diagnostic yield for monogenic diseases. Notably, recent evidence indicates that whole-exome sequencing provides actionable information leading to multiple molecular diagnoses in approximately 4.9 % of relevant cases [4]. In this context, we present a case of a female patient diagnosed with Down syndrome, characterized by profound intellectual disability, limited verbal communication, microcephaly, chronic fatigue, recurrent infections, and a progressively deteriorating motor condition marked by dyskinesia and hypertonia. Upon conducting metabolite analysis coupled with Trio-whole exome sequencing, we identified the presence of Combined methylmalonic acidemia and homocystinuria (Combined MMA and HCU) in addition to DS, thus elucidating the complexity of her clinical presentation. This discovery underscores the importance of comprehensive genomic testing to unravel hidden comorbidities in DS patients, ultimately informing targeted interventions and improving overall care management (see Fig. 1).

2. Case presentation

2.1. Subject

A Chinese Han female patient was delivered via cesarean section at 38 weeks of gestation, weighing 2900 g at birth. Her 33-year-old mother had undergone prenatal screening for DS during pregnancy, indicating a low-risk result. Despite an otherwise unremarkable gestation period free of complications, the infant presented with significant language and motor developmental delays from an early age. She attained independent sitting at 13 months but lacked crawling ability. Speech acquisition was notably delayed, with the child initially speaking indistinctly at 19 months, restricted to terms such as "mom," "grandma," and "aunt," and demonstrating limited language comprehension. By 24 months, concerns about her inability to walk prompted a consultation at our center. The pediatrician recognized facial features consistent with Down Syndrome. Karyotype analysis confirmed the diagnosis with the presence of an extra copy of chromosome 21 (Fig. 2). Her global developmental delay was attributed to Down Syndrome by the pediatric team.

Post-diagnosis, the patient engaged in prolonged speech and motor rehabilitation, yet her language development failed to show improvement and regressed, with even familiar words like "mom" and "grandma" becoming lost. While she initiated walking at 30 months, her gross motor milestones, including running and jumping, were not met. By 67 months, her motor abilities significantly declined, evidenced by lower limb weakness and unstable gait. Following a month-long episode of recurrent upper respiratory infections at 79 months, she exhibited lethargy, reduced appetite, and a worsening of motor functions. Within a short span, she lost the capability to walk unaided, perform basic maneuvers such as rolling over, and required support to maintain a seated position.

Throughout her development, she persistently demonstrated poor mastication, preferring soft foods and avoiding protein-rich items like meat, eggs, and milk. Her parents and siblings were all healthy, with no reported familial history of genetic diseases.

At 81 months, a comprehensive physical examination (Fig. 3) revealed her height and weight to be 120cm and 20kg respectively, placing her between −1 standard deviation (SD) and the mean for both measures, and her head circumference was 47.8cm, falling between -1SD and -2SD. Characteristic facial features included upslanted palpebral fissures, epicanthal folds, a flat nasal bridge, a small oral aperture, low-set and prominent ears, a flattened occiput, and a simian crease. Neurological and musculoskeletal assessments disclosed diminished muscle strength throughout her limbs, heightened lower limb muscle tone, hyperactive knee jerks bilaterally, positive ankle valgus bilaterally, and abnormal pes planovalgus and varus deformities.

Radiographic investigations of the hip and knee joints detected no bony abnormalities, except for a bilateral cervical Cobb angle of 153°. In Electrophysiological studies, there was a predominant affection of peripheral motor fibers in all four limbs, particularly pronounced in the lower limbs (Table 1). Notably, sensory nerve conduction in all extremities remained intact. Magnetic resonance
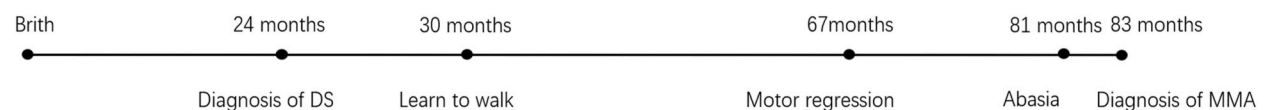
Fig. 1. Timeline of the motor development in the subject with DS and combined MMA and HC.
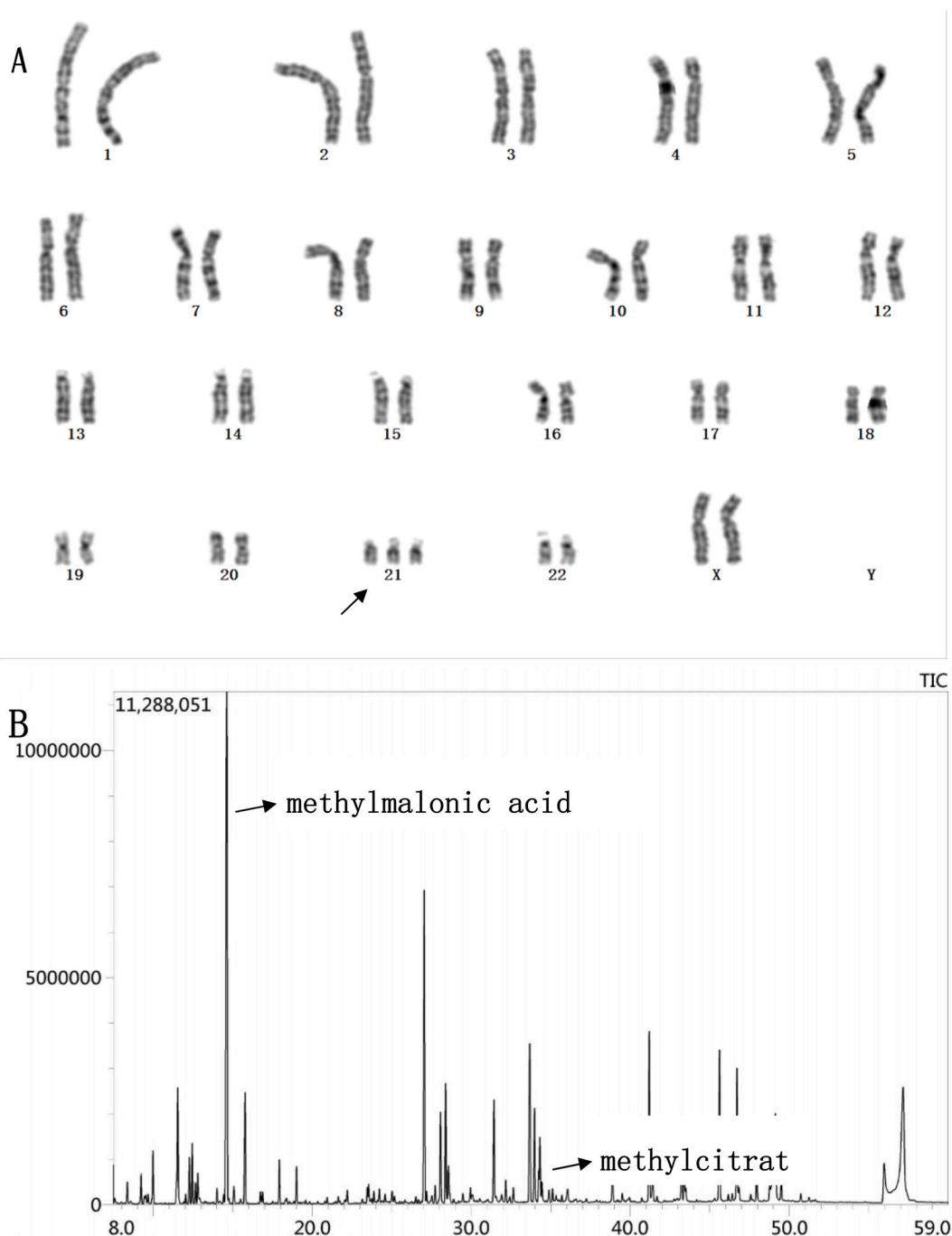
Fig. 2. (A) Karyotype analysis of the subject, showing a trisomy of chromosome 21 (47, XX, +21), confirming the diagnosis of Down Syndrome. (B) GC/MS profiling of organic acids in the subject, revealing significantly increased levels of methylmalonic acid and methylcitric acid.

imaging (MRI) of the brain and spine disclosed widened and deep sulci in the bilateral cerebellar hemispheres, enlarged extracerebral fluid spaces, a large cisterna magna, and a slightly attenuated spinal cord. Blood chemistry, plasma ammonia, lactic acid, hematological analyses, and echocardiography findings were all within normal limits. Notably, serum homocysteine levels were significantly elevated at 161.7 μmol/L (normal reference range: 0–15 μmol/L), suggesting an additional metabolic concern.

2.2. Metabolic analysis and genetic testing

Blood amino acids and carnitine from dried blood spots were measured by liquid chromatography–tandem mass spectrometry (LC-
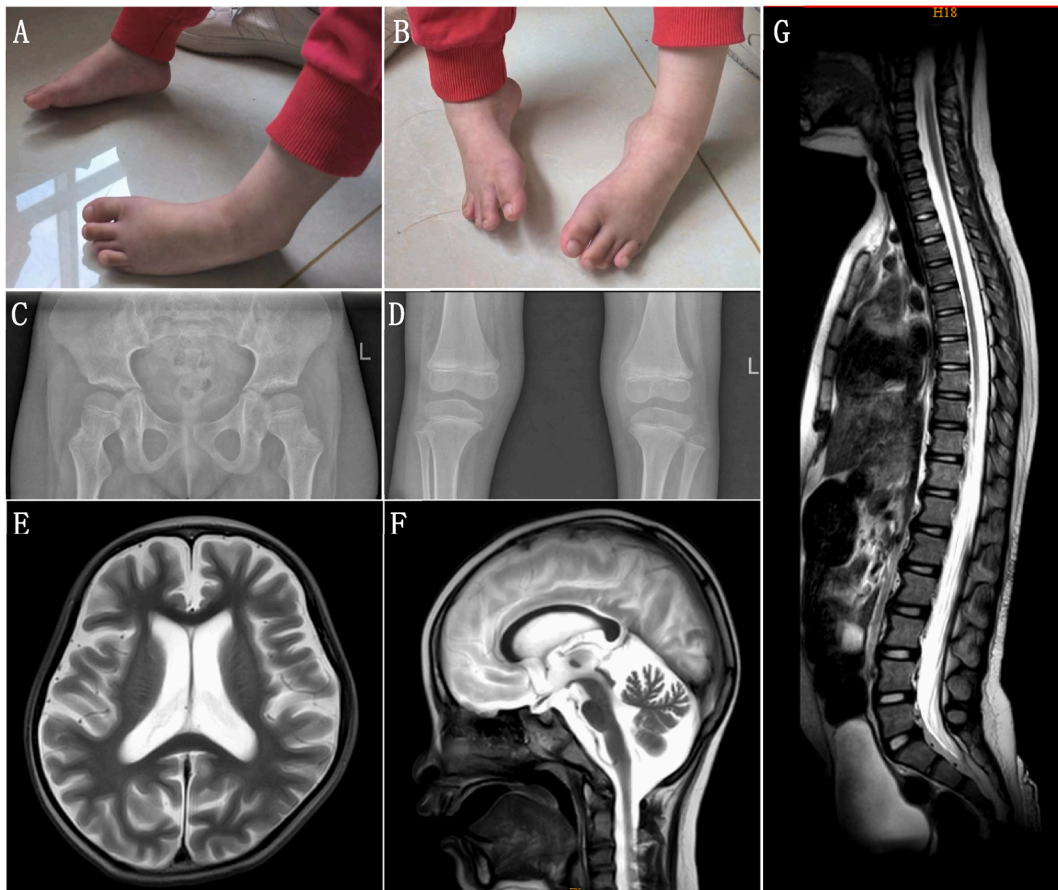
Fig. 3. (A–B) Subject exhibits abnormal drooping and varus feet postures. (C–D) Hip and knee joint X-rays reveal no bony irregularities, except for a bilateral cervical Cobb angle of 153°. (E) MRI demonstrates profound and extensive sulcal widening across all lobes of both cerebral hemispheres. (F) Deep and wide cerebellar sulci along with a large cisterna magna are evident. (G) Spinal cord appears slightly attenuated.

MS/MS) using an Applied Biosystems API 3200 analyzer (ABSCIEX, Foster City, USA) and ChemoView software (ABSCIEX, Foster City, USA). The results showed that methionine was 4.22 μmol/L (reference range 8–50μmol/L), free carnitine (C0) was 4.82 μmol/L (reference range 7–51.4μmol/L), acetylcarnitine (C2) 5.31 μmol/L (reference range 9–50μmol/L), propionyl carnitine (C3) 2.68 μmol/L (reference range 0.5–4.7μmol/L), C3/C0 0.56 (reference range 0.01–0.20μmol/L), C3/C2 0.51 (reference range 0.03–0.20μmol/L). The urine organic acids were analyzed by gas chromatography–mass spectrometry (GC/MS) using a GCMS-QP2010 analyzer (Shimadzu, Tokyo, Japan) and Inborn Errors of Metabolism Screening System Software (Shimadzu, Tokyo, Japan). The results showed that methylmalonic acid and methylcitrate were significantly higher than normal, 107.6 (reference range 0.0–4.0) and 4.4 (reference range 0.0–0.7), respectively (Fig. 2).

Whole exome sequencing was used to detect possible genetic variants in the patient and her parents. gDNA (500ng) was captured with the IDT xGenExome V2 reagent (Integrated DNA Technologies, Inc., Lowa, USA) and sequenced (Illumina Novaseq 6000, 150 base paired-end reads; Illumina, Inc., California, USA). Raw data was then quality filtered to generate "clean reads" for further analysis. The clean reads were then aligned to the human genome reference (hg19) using the Sentieon software package. over 99 % coverage of genes was achieved, with an average base depth of over 150, We used picard compared the results to remove redundancy and passed the result to the Sentieon-GATK to detect Single Nucleotide Variations and indels. All previously identified SNVs and indels were determined using multiple databases, including the NCBI dbSNP, HapMap, the 1000 Genomes Project, the Exome Aggregation Consortium. The Human Gene Mutation Database (HGMD) was used to identify any variant reported as pathogenic in published studies. The remaining variants were then assessed under the protocol issued by ACMG. 17 Alamut® Software Suite (Interactive Biosoftware, Rouen, France) and Ensembl (http://www.ensembl.org/) and were used for assessing pathogenicity. An in-house algorithm was used for exon-based Copy Number Variation (CNV) detection and a misalignment detection algorithm [5] is used for pseudogene's optimization.

Genetic analysis uncovered compound heterozygous variants in the *MMACHC* gene (NM_015506.3) in the proband: a paternal-origin variant c.217C > T (p.Arg73*), rs796051995, and a maternal-origin variant c.482G > A (p.Arg161Gln), rs121918243. According to ACMG classification criteria, p.Arg73* was classified as pathogenic based on several lines of evidence: PVS1, as it introduces a premature stop codon at the 73rd amino acid residue likely causing truncated protein, supported by multiple reported cases

Table 1

Motor nerve conduction study results in the subject's electrophysiological assessment.

Motor nerve	CMAP		
	dL (ms)	amplitude (mV)	MNCV(m/s)
Right median nerve			
Wrist-APB	3.0	11.6	NT
Elbow-wrist	6.4	9.6	47.1
Left median nerve			
Wrist-APB	3.0	10.9	NT
Elbow-wrist	6.3	9.8	48.5
Right ulnar nerve			
Wrist-ADM	1.67	9.4	NT
Elbow-wrist	4.9	7.5	49.5
Left ulnar nerve			
Wrist-ADM	2.0	10.0	NT
Elbow-wrist	5.0	9.1	50.0
Right musculocutaneous nerve			
Erb's-Biceps	3.7	**3.8**	NT
Left musculocutaneous nerve			
Erb's-Biceps	3.9	**4.0**	NT
Right radial nerve			
Elbow-EDC	2.4	9.0	NT
Brachiu-Elbow	3.6	8.0	66.7
Left radial nerve			
Elbow-EDC	2.6	9.6	NT
Brachiu-Elbow	3.8	8.9	66.7
Right tibial nerve			
Ankle-AHB	3.2	**8.7**	NT
Poplite-Ankle	9.0	**7.0**	**38.8**
Left tibial nerve			
Ankle-AHB	3.2	**5.8**	NT
Ankle-Ankle	3.4	**5.8**	NT
Poplite-Ankle	9.6	**5.1**	**36.3**
Poplite-Poplite	9.9	**5.2**	NT
Right peroneal nerve			
Ankle-EDB	2.6	**1.7**	NT
Fibula-Ankle	8.7	**2.0**	**39.3**
Left peroneal nerve			
Ankle-EDB	3.2	**1.7**	NT
Fibula-Ankle	9.1	**1.7**	**40.7**
Right femoral nerve			
Inguina-RF	3.0	**6.2**	NT
Inguina-Inguina	2.9	**6.2**	NT
Left femoral nerve			
Inguina-RF	3.0	**6.2**	NT
Inguina-Inguina	3.0	**6.3**	NT

Note: Skin temperature was maintained at 32 °C. Abbreviations: ADM, abductor digiti minimi; AHB, abductor hallucis brevis; APB, abductor pollicis brevis; Biceps, biceps brachii; Brachiu, brachioradialis; CMAP, compound motor action potential; dL, distal latency; EDB, extensor digitorum brevis; EDC, extensor carpi radialis; MNCV, motor nerve conduction velocity; mV, millivolt; NT, not tested; RF, rectus femoris. The data in boldface type indicated abnormal data.

downstream of this variant in the HGMD database; PM3_VeryStrong, since this variant has been found in homozygous or compound heterozygous states in numerous Methylmalonic acidemia (MMA) patients; and PM2_Supporting, given its extremely low frequency of 0.000004 in the gnomAD control population. Regarding p.Arg161Gln, substitution of arginine to glutamine at the 161th position of *MMACHC* was deemed pathogenic following ACMG guidelines due to: PM3_VeryStrong, as it has been documented in MMA patients in homozygous or compound heterozygous status; PM5, considering a neighboring variant at the same position, p.Arg161Gly, is listed as pathogenic in the HGMD; PS3_Moderate, because functional assays demonstrated that p.Arg161Gln reduces MMACHC stability and its binding affinity to cyanocobalamin (CNCb1); and PP3, which is predicted deleterious by multiple bioinformatics tools.

2.3. Outcome and follow-up

The diagnosis established the presence of DS concurrent with a metabolic disorder linked to variants in the *MMACHC* gene, manifesting as a combined MMA and HC phenotype. Upon initiation of a two-month treatment protocol involving intramuscular injections of methylcobalamin (administered at a dosage of 1 mg every other day) and oral intake of ʟ-carnitine (at a daily dose of 1 g), the patient manifested substantial recovery in motor function, as evidenced by their newfound ability to sit unsupported and execute lateral body turns. Additionally, a discernible decrease in the hypertonia of the lower limbs signified a restoration of muscle tone and enhanced motor control. Nonetheless, unsupported standing and independent walking remained unachievable. Bloodwork revealed

normal levels of C0 and C3 post-treatment, concurrent with a reduction in homocysteine levels to 48.1 μmol per liter. Moreover, urinary excretion of methylmalonic acid and methylcitrate diminished to 25.9 and 1.2 units, respectively. It is noteworthy that caregivers documented a swift alleviation of lethargy following the onset of treatment. Subsequently, however, a week into the therapy, the patient experienced augmented neurological excitability, manifesting as a reduced nocturnal sleep duration of merely 3–4 hours without any daytime napping. In response to these developments, we substituted methylcobalamin with hydroxocobalamin, which resulted in resolution of the patient's sleep disturbance. This intervention effectively addressed the emergent issue of heightened neurological excitability and restored more normalized sleep patterns.

3. Discussion and conclusions

Despite the association with intellectual disability, most people with DS develop language and many learn to read and are able to work independently with little support [6]. About 10 % of children with DS can sit up straight and exhibit independent walking patterns by 3 years of age, and about 95 % of children show these abilities between 3 and 6 years of age. In general, children with DS retain the typical sequence of motor development, but basic motor skills such as walking, running, jumping, climbing, throwing, and catching are acquired later in childhood [7]. Over the past 20 years, an increasing number of people with DS have been reported to have acute or subacute neurocognitive deterioration, usually previously diagnosed with "late-onset" ASD or "early-onset" Alzheimer's disease, now known as Down Syndrome Degenerative Disorder (DSRD). This condition typically manifests around the median age of 12–17 years, a critical factor in diagnosing DSRD [8]. Although cerebral atrophy, characterized by volume reduction in the frontal and temporal lobes, hippocampus, and amygdala, is commonly observed in individuals with Down syndrome and associated with varying degrees of cognitive and motor impairments, the rapid decline in motor function and the severity of motor abnormalities seen in this particular case, especially in the absence of DSRD, ischemic or hemorrhagic cerebrovascular disease, or pelvic organ hypoplasia, suggests an atypical pathophysiology not directly attributable to DS itself [9]. The metabolic investigation, which uncovered combined methylmalonic acidemia and homocystinuria, upon whole exome sequencing, provides a compelling alternative explanation for the unusual presentation of her motor deficits. Thus, while DS contributes to the spectrum of her clinical manifestations, the complex heterozygous mutations in the *MMACHC* gene, leading to the aforementioned metabolic disorder, play a pivotal role in understanding the unique aspects of her motor dysfunction.

MMA is a congenital disorder stemming from genetic defects affecting enzymes integral to the metabolism of methylmalonic acid and cobalamin [10]. CblC defect represents the predominant cobalamin metabolic defect, with its causative gene *MMACHC* located at chromosome 1p34.1. About 90 % of individuals with cblC defect exhibit severe manifestations during infancy, characterizing an early-onset phenotype; While late-onset cblC cases are relatively infrequent and manifest with a broad spectrum of symptoms that tend to evolve with advancing age [11–13]: neuropsychiatric symptoms often constitute the initial presentation in school-aged or adolescent patients with late-onset cblC; proteinuria/hematuria, glomerulopathies and progressive pulmonary hypertension predominate in preschool children, whereas thrombosis, neuropathy, and myelopathy are more commonly observed in adults. Wang et al.'s study [11], examining 26 late-onset cblC patients, uncovered through electromyographic that 80 % exhibited signs of peripheral nerve damage, while MRI scans frequently depicted diffuse atrophy of both the cerebral and cervical spinal cord along with bilateral hyperintensities in the deep white matter and cerebellum in this patient cohort. Notably, the c.482G > A mutation is the most recurrent allele in the late-onset cblC population and has been associated with a milder clinical course; however, exceptions exist, as one patient homozygous for the c.482G > A variant displayed early-onset symptoms [12,13]. In light of previous literature [14], there exists a case of a cblC patient whose phenotypic expression, characterized by the onset of lower limb weakness at 31 years old, and genotypic profile, represented by compound heterozygous mutations in the *MMACHC* gene (c.482G > A and c.217C > T), align closely with the patient described in this study. This concurrence serves to emphasize the potential for late-onset cblC disease to present as an acute and progressive polyneuropathy, a critical observation that enriches the scholarly discussion on the diverse clinical manifestations of this disorder.

Obstructive sleep apnea (OSA) is a prevalent sleep issue among DS patients, with an almost 100 % prevalence rate in adolescent and adult patient populations [15]. Furthermore, pediatric DS populations often experience bedtime resistance, sleep anxiety, night awakenings, disrupted sleep patterns, and excessive daytime somnolence [16]. Similarly, lethargy is a frequently observed neurological symptom in patients with Combined MMA and HCU [17]. In the scrutinized case, the sleep disturbances remained a significant aspect throughout the clinical trajectory, evolving from profound pre-treatment lethargy to notably diminished sleep following intervention. The prompt resolution of lethargy following methylcobalamin administration allowed us to swiftly correlate it to Combined MMA and HCU as a secondary effect. However, the persistence of diminished sleep despite treatment led to conjecture on a potential link with intramuscular methylcobalamin use. This hypothesis gained traction when the patient's sleep time normalized rapidly upon switching to hydroxocobalamin. Notably, there is no existing literature suggesting methylcobalamin induces increased excitability or sleep diminution in Combined MMA and HCU patients. This finding underscores the possibility of substantial individual variation in response to methylcobalamin treatment among Combined MMA and HCU patients and emphasizes the critical need for meticulous monitoring and evaluation of sleep patterns during such therapy.

This case, albeit serendipitous, advocates vigilance for comorbidities and comprehensive diagnostics in patients with established genetic disorders. The convergence of neurological phenotypic expressions heightens the risk of overlooking critical symptoms, which could inadvertently result in delayed interventions and consequent irreversible neural damage.

Data availability statement

The raw sequence data reported in this paper have been deposited in the Genome Sequence Archive (Genomics, Proteomics & Bioinformatics 2021) in National Genomics Data Center (Nucleic Acids Res 2022), China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences (GSA-Human: HRA007367) that are publicly accessible at https://ngdc.cncb.ac.cn/gsa-human.

Funding information

Ethics declarations

This study was reviewed and approved by the Medical Ethics Committee of Children's Hospital Affiliated to Shandong University (Jinan Children's Hospital) with the approval number: SDFE-IRB/P-2022015, dated July 18, 2022. Written informed consent for the participant's involvement in the study and the dissemination of their data was obtained from her legal guardians, considering the participant, aged under 10, did not possess the legal competence to independently provide informed consent.

CRediT authorship contribution statement

Rui Dong: Writing – original draft, Project administration, Conceptualization. **Chen Liu:** Investigation, Formal analysis, Data curation. **Yulin Liu:** Software, Methodology. **Haiyan Zhang:** Validation, Resources. **Guohua Liu:** Supervision. **Yi Liu:** Writing – review & editing. **Zhongtao Gai:** Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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