CASE REPORT

Clinical Research on Rett Syndrome: Central Hypoxemia and Hypokalemic Metabolic Alkalosis

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ABSTRACT

Background • Rett syndrome (RTT) is now widely recognized as a profound neurological disorder that predominantly affects females and is closely associated with mutations in the methylated CpG binding protein 2 (*MECP2*) gene located on the X chromosome. The Characteristic symptoms of RTT include the loss of acquired language and motor skills, repetitive hand movements, irregular breathing, and seizures. Additionally, RTT patients may experience sporadic episodes of gastrointestinal problems, hypoplasia, early-onset osteoporosis, bruxism, and screaming episodes. It is worth noting that males exhibit a unique and variable phenotype, though rare in RTT cases, often accompanied by severe manifestations.

Case Presentation • In this report, we present the case of a young male child with a de novo c.806delG hemizygous mutation, leading to an atypical presentation of RTT that remarkably mirrors the clinical features of Bartter syndrome, a genetic metabolic disorder. The clinical manifestations in this case included the loss of previously acquired language and motor skills, repetitive hand movements, breathing irregularities, seizures, sporadic episodes of gastrointestinal distress, hypoplasia, early-onset osteoporosis, bruxism, and episodes of screaming. This distinctive presentation underscores the complex diagnostic landscape of RTT, particularly in males, and highlights the need for vigilant clinical evaluation.

Conclusions • This case report sheds light on an unusual and atypical presentation of RTT in a young male child with a de novo c.806delG hemizygous mutation. The resemblance of clinical features to Bartter syndrome underscores the diagnostic challenges posed by RTT and highlights the importance of comprehensive clinical assessment and genetic testing, especially in cases deviating from the typical RTT phenotype. Our findings contribute valuable insights into the early diagnosis and management of atypical RTT presentations. (*Altern Ther Health Med.* 2024;30(1):167-171).

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INTRODUCTION

Rett syndrome (RTT) is a neurodevelopmental disorder[1-2] primarily attributed to the functional deletion of the methylated CpG binding protein 2 gene (*MECP2*) on the X chromosome.[3-5] This syndrome was initially identified in 1966 by Mr. Andreas Rett, an Austrian pediatric neurologist,[1] marking the world's first documented case of RTT. Later, RTT cases have been reported across the globe.

Given its rarity, phenotypic diversity, and heightened severity in male patients, RTT's early identification and diagnosis hold paramount clinical significance. The syndrome's diagnosis hinges upon a combination of clinical manifestations and genetic testing. A clinical diagnosis of RTT relies on a comprehensive set of well-defined inclusive and exclusive criteria. To be considered a typical RTT diagnosis, it must satisfy both the inclusive and exclusive criteria.[3-5]

The inclusive criteria include specific features such as impaired hand skills, loss of acquired spoken language, gait abnormalities, and stereotyped hand movements. In contrast, the exclusion criteria comprise conditions such as brain injury secondary to trauma (perinatal or postnatally), neurometabolic disease, or severe infections leading to neurological issues. Additionally, the presence of grossly

abnormal psychomotor development within the first 6 months of life is considered an exclusion criterion. Characteristic symptoms of RTT comprise the loss of acquired language and motor skills, repetitive hand movements, respiratory irregularities, and seizures.

Patients diagnosed with RTT may also experience sporadic episodes of gastrointestinal problems, hypoplasia, early-onset osteoporosis, bruxism, and episodes of screaming.[6-7] While RTT predominantly results in severe intellectual disability in females, with an estimated incidence ranging from approximately 1 in 15 000 to 1 in 10 000,[8-9] it is notably rare in males.[10] The primary clinical manifestations comprise the loss of acquired motor, language, and hand skills, along with stereotypic movement patterns, epilepsy, and respiratory disorders.[11]

Bartter syndrome is an autosomal recessive disorder characterized by renal tubular dysfunction, primarily presenting as hypokalemic metabolic alkalosis and the activation of the renin-angiotensin-aldosterone system. The condition is attributed to a mutation in the *CICNKB* gene, which encodes a potassium ion channel within the renal tubules. Bartter syndrome is associated with a generally unfavorable prognosis.[12-13]

In this case study, the primary clinical feature observed in the child closely resembled hypokalemic metabolic alkalosis, reminiscent of Bartter syndrome. A comparative analysis was conducted to assess the clinical manifestations and molecular genetics of both conditions. Bartter syndrome is categorized into five distinct forms based on molecular genetics, specifically *SLC12A1*, *KCNJ1*, *CLCNKB*, *BSND*, and *CLCNKA+CLCNKB*, as well as *MAGED2*. However, genetic testing in the present case revealed an *MECP2* mutation, implicating an atypical RTT diagnosis in accordance with international RTT clinical diagnostic standards.

There is scarcity in literature as only a limited number of reports focusing on atypical RTT cases are present. Male presentations are particularly rare and demonstrate diverse phenotypes along severe symptoms.[14] Therefore, this report provides a comprehensive account of the clinical features observed in a male case of atypical RTT, offering valuable insights for early diagnosis.

CASE PRESENTATION

Patient History

In 2020, a 3-month-old male child was admitted to the Pediatric Respiratory Department of our hospital due to a persistent cough that lasted for over a month. The child's cough was ongoing for over a month without any identifiable triggers. His body temperature remained within the normal range, and he presented with an intermittent monophonic cough characterized by its mild, infrequent, and dry nature. Since the onset of symptoms, the child exhibited a generalized change in mental state and reduced appetite. Despite these symptoms, his urine and stool remained normal. Notably, the child recently experienced a weight loss of 500 grams in this condition.

Table 1. Blood Gas Analysis Results During Hospitalization

No.	Days of Hospitalization	pH	PO_2 (mmHg)	PCO_2 (mmHg)	BE (mmol/L)	HCO_3^- (mmol/L)	K (mmol/L)	Na (mmol/L)	Ca (mmol/L)
I	6	7.49	82	56	17.10	42.70	2.7	137	0.79
II	7	7.47	99	62	18.91	45.10	2.9	136	0.88
III	8	7.51	104	56	19.50	44.70	4.4	136	1.22
IV	9	7.42	82	69	18.30	44.80	2.6	139	0.89
V	10	7.57	128	48	20.00	44.00	3.5	136	0.75
VI	12	7.54	76	46	14.90	39.30	3.4	134	1.25
VII	15	7.51	59	40	8.20	31. 90	3.7	134	1.14

Note: Rows I-V represent arterial blood samples; Rows VI-VII represent venous blood samples.

Abbreviations: pH, pH level of blood; PO_2, Partial pressure of oxygen in mmHg; PCO_2, Partial pressure of carbon dioxide in mmHg; BE: Base excess in mmol/L; HCO_3^-, Bicarbonate concentration in mmol/L; K, Potassium concentration in mmol/L; Na, Sodium concentration in mmol/L; Ca, Calcium concentration in mmol/L.

Family and Medical History

After birth, the infant underwent hospitalization on three separate occasions. The admissions were attributed to neonatal pneumonia, hypoxic-ischemic encephalopathy, and bronchopneumonia caused by meconium aspiration syndrome. Importantly, there was no recorded history of allergies. The child's mother experienced three pregnancies and gave birth to two children. In the family's medical history, there was no documented presence of hereditary diseases, and none of the family members exhibited similar symptoms.

Clinical Examination Findings

During the examination, the patient's vital signs were recorded as follows: a temperature of 36.6°C, a heart rate of 109 bpm, a respiratory rate of 20 breaths per minute, a blood pressure of 76/46 mmHg, a weight of 4.2 kg, a head circumference of 37 cm, and a pulse oxygen saturation ranging between 89% and 92%. The patient exhibited consciousness but displayed a weak response to external stimuli.

Physical examination revealed thin subcutaneous fat and a flat, soft fontanel. Auscultation of both the heart and lungs yielded normal findings. Additionally, there were observations of low muscle tension in the extremities, primarily characterized by a limited ability to lift the head without any discernible pathological signs.

Laboratory and Diagnostic Findings

Different laboratory tests were performed, and the following findings were observed: (1) Blood Analysis: Blood analyses indicated a hemoglobin level of 82 g/L, with all other parameters falling within the normal range. Bowel and urine functions were also within the normal range. A blood gas analysis revealed the presence of metabolic alkalosis, concurrent with respiratory acidosis and hypokalemia, refer to Table 1. (2) Biochemical Profiles: Hepatic and renal functions showed normal albumin levels of 34.8g/L and globulin levels of 12.1 g/L. Myocardial enzymes and cerebrospinal fluid test results were within the normal range.

(3) Immunological Assessment: Immune function analysis demonstrated completeness, with C3 levels at 0.60 g/L and C4 levels at 0.11 g/L, while other parameters

remained normal; (4) Urine and Fluid Analysis: Urine organic acid analysis indicated elevated levels of 2-hydroxybutyric acid. Pathogen screening from sputum and alveolar lavage fluid cultures revealed no pathogens. (5) Clinical Examinations: Laryngoscopy revealed mild laryngomalacia, and bronchoscopy showed purulent secretions. The electrocardiogram displayed sinus arrhythmia with incomplete right bundle branch block.

(6) Neurological Findings: The electroencephalogram (EEG) displayed abnormal patterns, including low, slow, sharp waves from the frontal region of the head and θ rhythmic patterns during sleep, refer to Figure. 1. (7) Radiological Imaging: Computed Tomography (CT) scans showed inflammatory lung lesions in the inferior lobes of bilateral lungs, refer to Figure 2, while a CT scan of the head showed no obvious abnormalities. Color Doppler echocardiography revealed a 2.7mm atrial septal defect. (8) Parental Decision: The parents declined magnetic resonance imaging (MRI) of the head.

Molecular Analysis

After acquiring parental informed consent, the proband and his parents underwent trio-whole-exome sequencing (WES). In the proband, a de novo c.806delG hemizygous mutation ([HG19] chrX:153296473) was identified within exon 4 of *MECP2* and subsequently validated through Sanger sequencing. No mutations were detected at the relevant locus in the parents, confirming that the mutation in the patient was a novel occurrence. This finding also explained why the parents remained asymptomatic while their child exhibited related symptoms and signs.

Mutation Characterization. The amino acid coding mutation (p.G269Afs) (NM_004992) resulted from a single base G deletion at position 806 (as illustrated in Figure 3). According to the diagnostic guidelines of the American College of Medical Genetics and Genomics (ACMG) (2015), this variation was classified as pathogenic (PM2+PP5+PS2+PVS1-s).

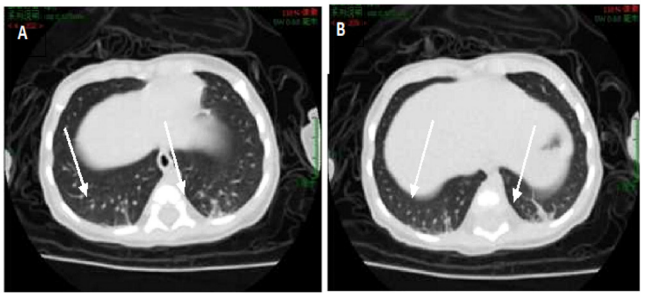
Final Diagnosis

Upon thorough examination, the child exhibited signs of malnutrition, intellectual retardation, and microcephaly. During the hospitalization period, a range of clinical manifestations emerged, including respiratory disorders, hypoxemia, convulsions, metabolic alkalosis, hypokalemia, and edema, akin to Bartter syndrome, a genetic metabolic disorder. However, genetic testing did not support a definitive diagnosis of Bartter syndrome.

Considering the genetic testing data in children with RTT and the clinical diagnostic criteria proposed in 2011,[8] a typical RTT diagnosis requires the fulfillment of four main criteria and exclusion criteria. This exclusion criterion mandates that the patient's age should exceed 6 months for a diagnosis. In our case, the child was younger than 6 months, rendering him ineligible for a typical RTT diagnosis.

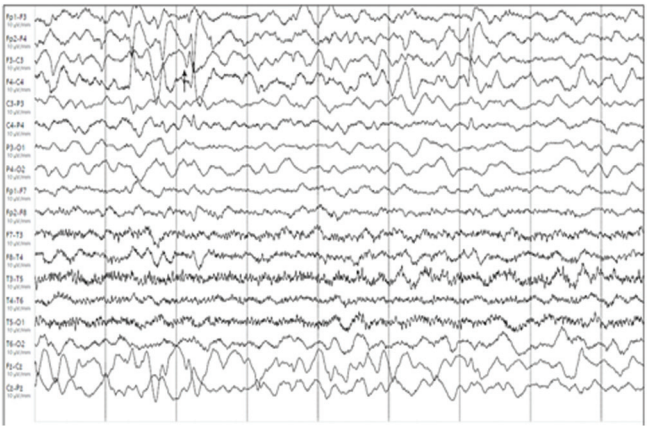
On the other hand, an atypical RTT diagnosis requires the satisfaction of at least two main and five supporting

Figure 1. EEG Patterns in the Child



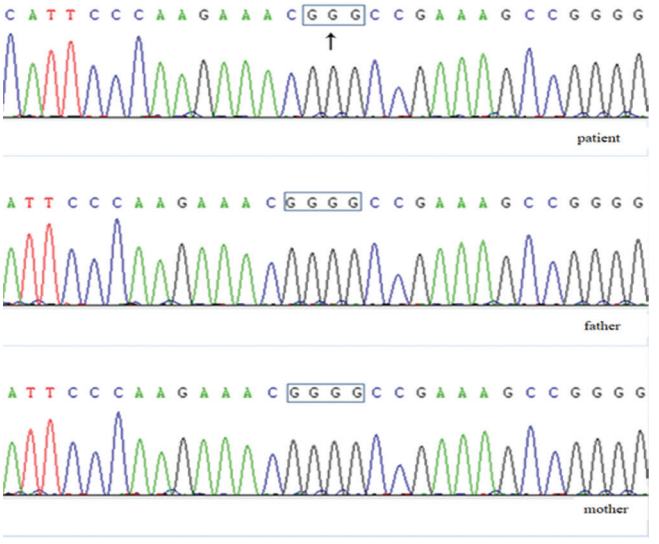
Note: In this EEG recording, observed are low, slow, sharp waves originating from the frontal region of the electroencephalogram (EEG). During sleep, distinctive frontal head θ patterns also appear. Arrows indicate slow and sharp waves for reference.

Figure 2. Lung CT Scan of the Child



Note: This lung CT scan reveals areas with notable lesions indicative of lung infection, as highlighted by the arrows for clear identification.

Figure 3. Mutation in Exon 4 of *MECP2* Gene in the Proband (C.806delG)



Note: This figure illustrates the specific mutation observed in exon 4 of the *MECP2* gene in the proband, represented as C.806delG.

criteria. In our case, the child met all five supporting criteria, encompassing respiratory disorders, sleep rhythm disorder, abnormal muscle tone, abnormal developmental delay, and decreased pain stimulation. However, due to the child's age of 3 months, whether he met the major criteria, including the loss of acquired speech and motor skills, and hand dysfunction, remained inconclusive. Consequently, we leaned toward categorizing the case as atypical RTT with a concurrent pulmonary infection.

Treatment Approach

After admission, the child received a comprehensive treatment regimen that included continuous positive airway pressure (CPAP) assisted ventilation, later switched to a nasal catheter with low-flow oxygen. Additionally, caffeine was administered to stimulate ventilation, anticonvulsant medications were provided, and anti-infective agents were prescribed to address potential infections. Efforts were made to correct alkali poisoning, and potassium supplementation was initiated to address hypokalemia. Diuretics were also employed as part of the treatment strategy. Furthermore, bronchoscopic alveolar lavage was conducted to address pulmonary concerns. Despite the administration of these treatments, the child continued to exhibit symptoms, including respiratory distress, hypoxemia, metabolic alkalosis, hypokalemia, and progressive systemic edema.

Outcomes and Follow-up

Since no clinical improvement was observed even after 12 days of hospitalization, the parents chose to discharge the child, and consequently, the follow-up was discontinued.

DISCUSSION

Our patient exhibited persistent slow breathing and hypoxemia. Notably, the patient displayed mild pulmonary symptoms, lacked obvious lung rales, and had small lesions on lung CT scans, which ruled out lung infection as the primary cause of respiratory distress. The presence of "difficult-to-correct metabolic alkalosis with hypokalemia" likely played a role in affecting respiration and blood oxygen levels.

Considering the patient's constellation of symptoms, including malnutrition, intellectual retardation, microcephaly, and convulsions, initial considerations pointed toward the possibility of Bartter syndrome.[15] This autosomal recessive disorder of renal tubular dysfunction is defined by distinct features, including hypokalemia, metabolic alkalosis, and activation of the renin-angiotensin-aldosterone system.[16]

The condition is linked to a mutation in a potassium ion channel gene (*CICNKB*) situated within the renal tubules. It is important to note that the prognosis for this disease is typically unfavorable. In this particular case, the child's parents declined to undergo examination of the renin-angiotensin-aldosterone system. The child's clinical presentation, marked by oliguria and edema, contrasted with the polyuria typically observed in Bartter syndrome and the renal tubular damage associated with the *CICNKB* mutation. Additionally, the child's genetic report revealed a *MECP2* mutation, leading to the consideration of a diagnosis of Pseudo-Bartter syndrome.[16-18]

Both Pseudo-Bartter syndrome and true Bartter syndrome share common symptoms such as hypokalemia, metabolic alkalosis, and activation of the renin-angiotensin-aldosterone system. However, unlike true Bartter syndrome, Pseudo-Bartter syndrome does not involve renal tubular damage.[17] Furthermore, there are no gene mutations associated with renal tubules in Pseudo-Bartter syndrome.

The clinical diagnosis of Pseudo-Bartter syndrome typically requires assessments of blood renin and aldosterone levels.[18] However, the child's blood renin and aldosterone measurements were unavailable in this case. Dehydration is the most likely explanation for the observed metabolic alkalosis in conjunction with respiratory acidosis and hypokalemia. The child's clinical presentation, including central nervous system (CNS) defects with respiratory involvement and hypokalemic metabolic alkalosis, indicates dehydration, possibly stemming from malnutrition.

The *MECP2* gene is situated on the X chromosome, classifying RTT as an X-linked dominant disorder. *MECP2* plays a crucial role in neuronal function. Consequently, RTT primarily affects females, as they possess a combination of cells expressing either the wild-type or mutant version of *MECP2* due to X chromosome inactivation. In contrast, males experience more severe manifestations of the disorder and are less likely to survive infancy.[19]

There are no definitive treatments for RTT, but symptom management can be enhanced through personalized, symptomatic, supportive therapy.[20-21] This approach incorporates a range of interventions, including physical therapy, speech training, music therapy, medications, surgical interventions, ketogenic diets, and other comprehensive treatments.[22] However, it is worth noting that current preclinical research has indicated promising possibilities for treating RTT.[19]

Ribeiro et al.[23] demonstrated that dietary vitamin D supplementation extended the shortened lifespan of *MECP2*-deficient mice by inhibiting NF-κB signaling. Additionally, Shulyakova et al.[24] revealed that interventions addressing mitochondrial dysfunction and oxidative stress hold promise as potential treatments for RTT.

In conjunction with genetic factors, contemporary treatment strategies primarily concentrate on two key areas: (1) identifying molecules in downstream pathways, These molecules are targeted to counteract the effects of *MECP2* deletion, and (2) genetic correction, This involves approaches such as gene therapy and protein replacement to rectify the genetic abnormalities associated with the disorder.

CONCLUSION

Rett syndrome remains a complex and not yet fully understood condition, characterized by a wide spectrum of clinical manifestations that present significant hurdles for early diagnosis. Nevertheless, genetic testing stands as the most

precise diagnostic method available. The internationally accepted diagnostic standard is the revised version proposed by the Clinical Research Association of Rett Syndrome in 2010. However, it is important to note that this standard may have limitations in diagnosing children under the age of 6 months.

In this case study, we have presented the clinical manifestations of atypical Rett syndrome in a male infant. It is worth noting that many of the manifestations of RTT are influenced by age, making the diagnosis in young children more intricate when compared to adults. Additionally, diagnosing male patients proves challenging due to the variability in clinical phenotypes, necessitating comprehensive differentiation from other disorders to prevent misdiagnosis. This case report contributes valuable insights to clinicians, aiding in the early and accurate diagnosis of RTT.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Ethics Committee of Maternal and Child Health Hospital of Hubei Province approved the research. The guardians of patients gave informed consent to participate in the study.

CONSENT FOR PUBLICATION

The guardians of patients gave informed consent for the publication of this study.

AVAILABILITY OF DATA AND MATERIALS

Relevant data is available on request from the corresponding author.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article.

FUNDING

This study did not receive funding in any form.

ACKNOWLEDGMENTS

We thank the study participants and their families for their cooperation.

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