Archives of Pediatrics
Alharbi R, et al. Arch Pediatr 9: 320
www.doi.org/10.29011/2575-825X.100320
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Case report

Isolated Adrenocorticotropic Hormone Deficiency Associated with Prolonged QT Interval in a Pediatric Patient: A Case Report and Review of Literature

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Citation: Alharbi R, Shaman BA, Alsubhi A, Aldubayee M, Alghamdi SA, et al. (2024) Infectious Causes of Hypopituitarism in Children: A Systematic Review. Arch Pediatr 8: 320. DOI: 10.29011/2575-825X.100320

Received Date: 26 December 2024; **Accepted Date:** 31 December 2024; **Published Date:** 06 January 2025.

Abstract

A 5-day-old baby girl was admitted to the pediatric intensive care unit (PICU) with non-ketotic hypoglycemia, abnormal movement, bradycardia, and a prolonged QT interval. Initial investigations, including whole exome sequencing, revealed a likely pathogenic variant in the TBX19 gene, which was associated with congenital isolated adrenocorticotropic hormone deficiency (ACTH). Upon initiating hydrocortisone treatment, there was significant improvement in the QT interval, indicating a potential link between cortisol deficiency and cardiac arrhythmias. Despite the initial success, the patient lost follow-up after discharge and was later readmitted at 16 months with recurrence of similar symptoms. Restarting hydrocortisone therapy resulted in improvements in electrocardiogram findings and her associated bradycardia. This case highlights the critical relationship between cortisol deficiency and prolonged QT interval and emphasizes the importance of early diagnosis and management of adrenal insufficiency in pediatric patients. The precise mechanisms underlying the association remain poorly understood, warranting further investigation into the role of glucocorticoids in cardiac function and the potential for life-threatening arrhythmias. This study aims to present this unique case and conduct a comprehensive literature review on the subject.

Keywords: Prolonged QTc interval; Hypoglycemia; TBX19; Hydrocortisone.

Introduction

A prolonged QTc interval, which can be inherited or acquired, poses a significant risk to the life of pediatric patients. Secondary causes are often linked to imbalances in electrolytes, medication usage or exposure to toxins. These causes may also be related to abnormal myocardial disease. In our case report, we discuss the connection between adrenocorticotropic hormone deficiency and a prolonged QTc interval. We observed that the QTc interval improved following treatment with hydrocortisone.

Case report

A 5-day old infant girl was admitted to the Pediatric Intensive Care Unit (PICU) due to non-ketotic hypoglycemia. She exhibited abnormal movements, bradycardia, and a progressive prolongation of the QT interval. Whole exome sequencing revealed a likely pathogenic variant in the TBX19 gene, which is associated with congenital isolated central adrenocorticotropic hormone (ACTH) deficiency. The patient was commenced on hydrocortisone treatment, resulting in an improvement of her QT interval length. However, after being discharged, the patient discontinued her medications without medical advice.

At the age of 16 months, she presented to the Emergency Room (ER) with seizures, fever, tachycardia, decreased level of consciousness and non-ketotic hypoglycemia. Her electrocardiogram (EKG) at that time showed sinus bradycardia, with a heart rate that could not be determined, and a QTc interval of 550 milliseconds (Figure 1A, 1B). She was readmitted to the PICU and hydrocortisone treatment was resumed. Biochemically, she exhibited adrenal insufficiency that did not meet the criteria for neither central or peripheral etiology. The patient's ACTH level was measured to be less than 1 pg/mol, and an ACTH stimulation test revealed a blunted response. Cortisol levels measured 30 and 60 minutes after the administration of ACTH consistently remained low. Thyroid-stimulating hormone (TSH) level was measured at 1.2 mlU/L, while the free thyroxine (T4) level was 12.6 pmol/L, and the free triiodothyronine (T3) level was 4.64 pmol/L.

Apart from the aforementioned EKG findings, an echocardiography showed a structurally normal heart with a small patent foramen ovale (PFO). Abdominal ultrasonography revealed a persistently thrombosed left portal vein, which did not require anticoagulant therapy. Following the reintroduction of hydrocortisone and levothyroxine, the QTc interval normalized once again.

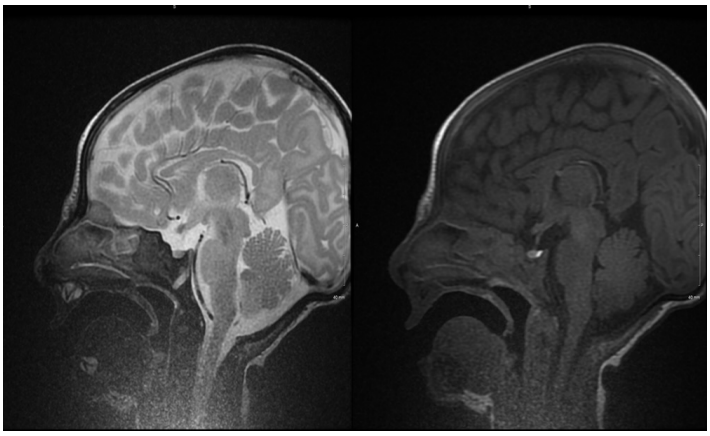

Figure 1A: Brain MRI.

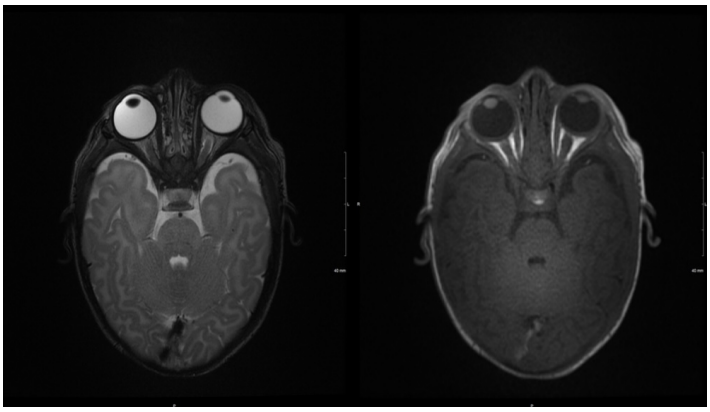

Figure 1B: Brain MRI.

Discussion

The exact mechanism underlying the association between cortisol deficiency and prolonged QT interval is not fully understood. Adrenal insufficiency can manifest in various ways, such as hypotension, hypoglycemia, and electrolyte imbalance. One crucial observation in this case is the presentation with fever associated with significant bradycardia, prolonged QTc interval and normal plasma electrolytes. Along with hypothyroidism and blunted ACTH challenging test showed low cortisol level. The direct effect of low glucose on the human Ether-à-go-go Related Gene (hERG) ion channel and hypokalemia has been reported to prolonged QT interval in individuals with type 1 and type 2 diabetes [1-5]. Glucocorticoid has been reported to be important for the maintenance of membrane calcium transport function in the cardiac sarcoplasmic reticulum [6]. It has been also reported that glucocorticoid up-regulates expression levels of various

ion channels, including IKs (mink, KvLQT1) and IKr (hERG, MiRP1) by inducing expressions of the serum- and glucocorticoid-inducible kinase (SGK1) [7]. Since these IK channels induce outward potassium currents, glucocorticoid deficiency may extend duration of action potentials by reducing expressions of SGK1 and these ion channels [5]. This prolongation improved dramatically after hydrocortisone administration. Our genetic testing revealed a pathogenic variant in the TBX19 gene that is associated with congenital isolated adrenocorticotropic hormone deficiency.

There are few reported cases of isolated adrenocorticotropic hormone deficiency that causes QT prolongation with no electrolytes disturbance. We searched the literature and no pediatric cases were reported in this regard. However, in adult patients we have found case about a 63-year-old lady with hypopituitarism and prolongated QTc interval that progressed to polymorphic VT. She had low cortisol, luteinizing hormone, follicle stimulating hormone, and prolactin with relatively low corticotropin, while having normal thyroid hormone and serum electrolytes. QTc length was normalized with hydrocortisone treatment [1].

Another case described a 44-year-old presented in cardiac arrest and EKG findings of polymorphic ventricular tachycardia and prolonged QTc interval.

Additional laboratory tests showed low baseline cortisol and ACTH levels. Corticotropin-releasing hormone, gonadotropin- releasing hormone and thyrotropin-releasing hormone stimulation tests were carried on and showed a poor response to CRH stimulation. On the other hand, ACTH stimulation was normal and she had high thyroid-stimulating hormone level. EKG findings improved after starting steroid and levothyroxine treatment [2].

One case reported about a 72-year-old man presented to the ER with altered level of consciousness and severe hypoglycemia. Earlier, he had nonvalvular chronic atrial fibrillation with preserved left ventricular ejection fraction. Then he suddenly collapsed with EKG showed that QT intervals were unexpectedly prolonged that progressed to torsade de pointes and ventricular fibrillation. His lab work was suggestive of cortisol deficiency. After starting hydrocortisone replacement therapy QTc was gradually normalized [3].

Although there are several genetic mutations causing a congenital long QTc interval but we did not find any in our patient as whole exome sequencing in 2019 and reanalysis of whole exome sequencing raw data in 2021 were both negative for variants causing such prolongation. Likely pathogenic mutation in TBX19 leading to DNA binding defects causing congenital isolated adrenocorticotropic hormone deficiency. Such patients will present with neonatal onset hypoglycemia and seizures. Biochemically; plasma cortisol and ACTH are low with diminished response to CRH. We believe that in this case the low serum cortisol caused the prolonged QTc.

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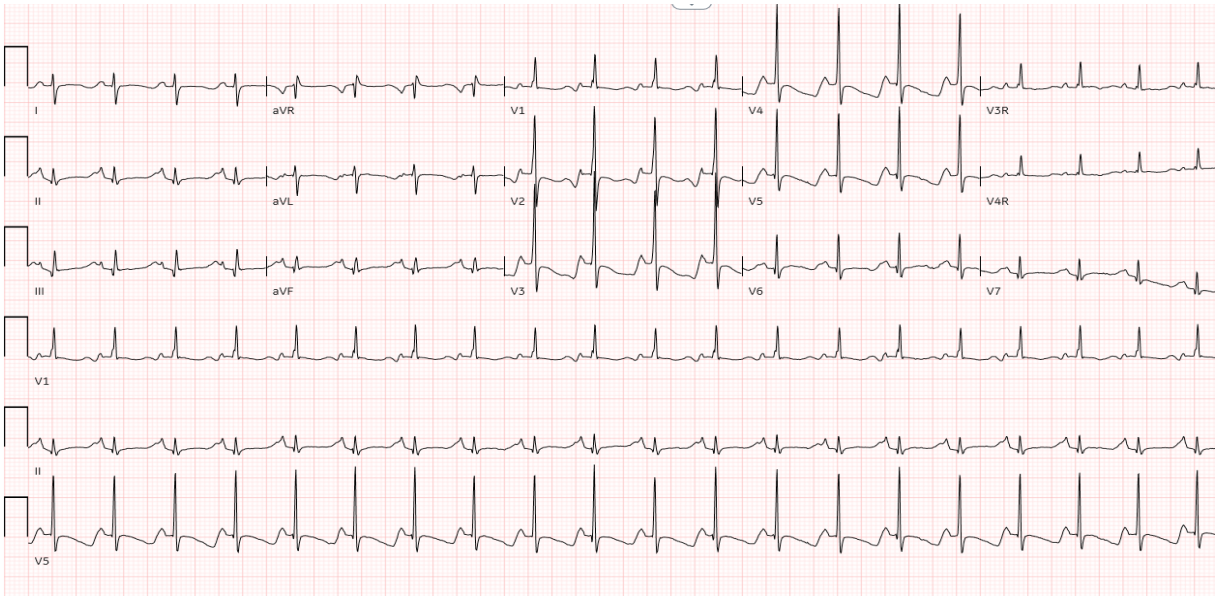

Figure 1: Sinus rhythm with diffusely flat T waves and prolonged QT interval, QTc 580m.

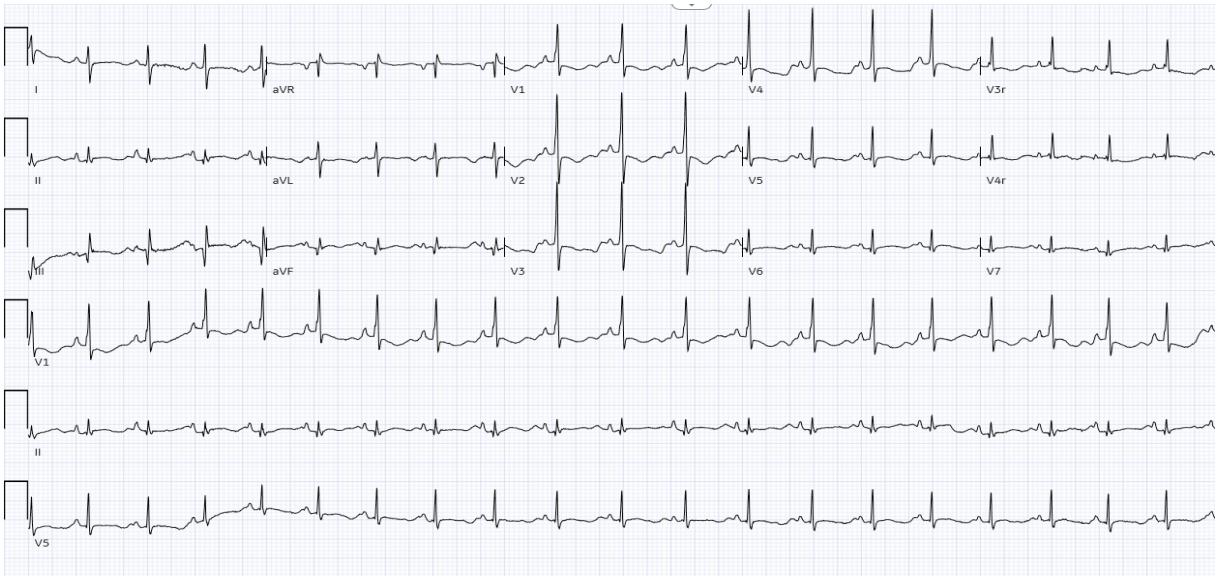

Figure 2: One day later with same finding of diffusely flat and inverted T waves in most of the leads more obvious sinus beats but still prolonged QTc > 580ms.

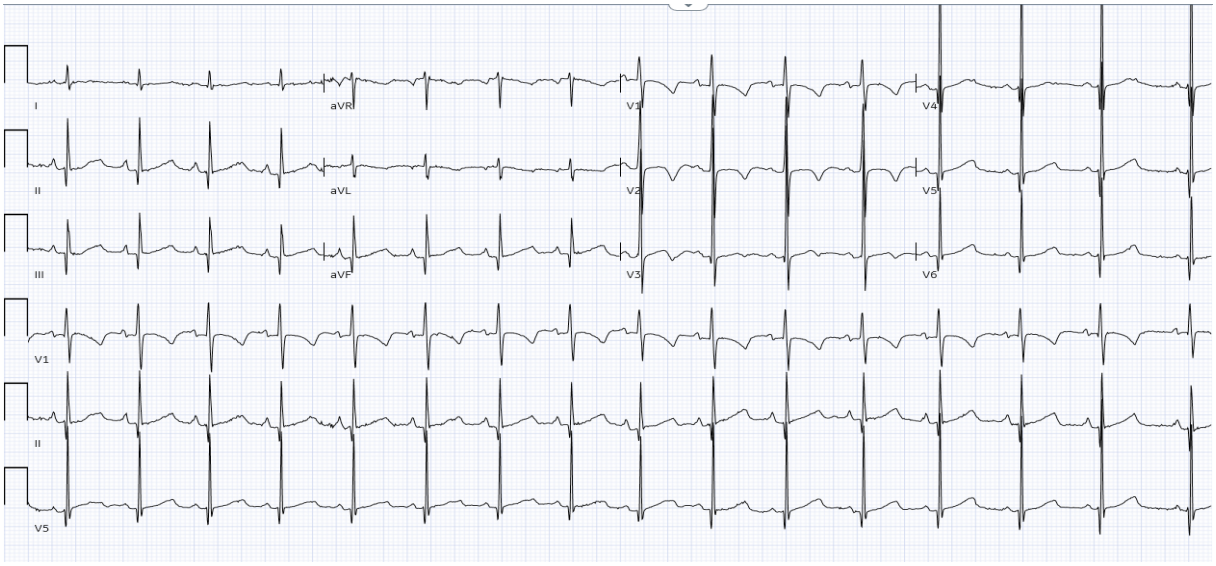

Figure3: Improved Qt interval after starting medications.

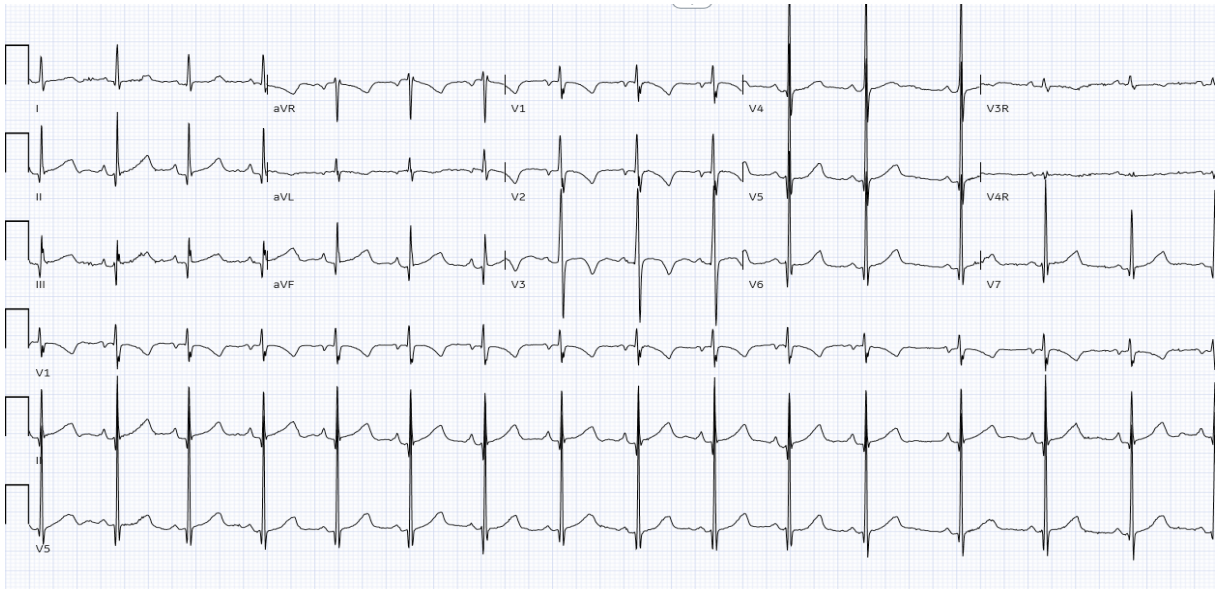

Figure 4: Normal sinus and normal QT interval at discharge.