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Case Report: Diabetes Mellitus as a Novel Endocrine Manifestation of Alpha Thalassemia X-linked Intellectual Disability (Atr-x) Syndrome

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Case Report

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Abstract

Background:

Alpha thalassemia/mental retardation X-linked (ATR-X) syndrome is a rare congenital disorder caused by mutations in the *ATRX* gene, predominantly affecting males and characterized by a broad spectrum of clinical features including intellectual disability, distinctive craniofacial/skeletal anomalies, urogenital malformations, and alpha thalassemia. Currently, dysglycemia and fulminant diabetes mellitus are not recognized as an endocrine-associated comorbidity of ATR-X syndrome.

Case Report:

This case report presents a 14-year-old male with ATR-X syndrome who presented with hypoactivity, increased secretion burden, and 3 days of fever admitted for evaluation and eventual management of recurrent pseudomonal tracheitis with intravenous (IV) antibiotics. Initial evaluation incidentally revealed marked hyperglycemia with a fasting plasma glucose of 320 mg/dL, prompting further evaluation that showed an elevated hemoglobin A1c (HbA1c) of 10.2% and mild ketosis without acidosis, consistent with diabetes mellitus. Type 1 diabetes-associated antibodies were ultimately negative, and his presentation was not consistent with other more common forms of diabetes, such as type 2 diabetes. As per relatives, the patient had polyuria, polydipsia, and unintentional weight loss of 15 pounds in the prior month. Family history was significant for a 20-year-old brother also with ATR-X syndrome who was diagnosed at 16 years of age with insulin-dependent diabetes of unknown etiology. The patient started basal-bolus insulin with adjustments based on glycemic trends as per continuous glucose monitoring (CGM) with improvements in his glucose levels throughout admission. He was discharged home on this regimen and a CGM.

Conclusions:

While not previously described in humans, murine models have demonstrated structural and inflammatory changes, associating *ATRX* deficiency with glucose dysregulation. Pancreatic histopathological findings include interlobular edema, ductal dilation, loss of lobular organization, ductal dysplasia, perivascular/peripancreatic/islet/acinar inflammation, hyperplasia of the islet cells, and fatty infiltration. These pancreatic findings in *ATRX*-deficient mice provide a plausible mechanism for the impaired glucose tolerance, dysregulated insulin secretion, and β-cell dysfunction seen in this case. In the end, this case suggests a possible mechanism between ATR-X syndrome and clinical diabetes not previously reported in humans. This report highlights the importance of consideration of and monitoring for diabetes mellitus in patients with ATR-X syndrome as a direct consequence of the syndrome itself.

1. Introduction

Alpha thalassemia/mental retardation syndrome X-linked (ATR-X) syndrome is a congenital disorder caused by mutations in the *ATRX* gene that encodes proteins responsible for chromatin organization essential for genomic stability and transcriptional regulation [1][7]. Its clinical phenotype is highly variable along a spectrum and, like most X-linked diseases, predominantly affects males. [1][6][8]. It is characterized by intellectual disability as the only universal feature while additional manifestations include craniofacial dysmorphism, microcephaly, short stature, musculoskeletal dysmorphisms, urogenital anomalies, and hematologic abnormalities such as alpha thalassemia [1][6][8].

Endocrine dysfunction in ATR-X syndrome most commonly involves growth and genital development, with diabetes mellitus not recognized as a typical or even a rare feature in current literature [1][8]. Diabetes mellitus has been reported as an endocrinological complication in some forms of alpha thalassemia, particularly in severe genotypes, and is thought to result from chronic iron overload causing direct impairment of insulin secretory function [2][9]. This differs from ATR-X syndrome, in which the associated thalassemia is typically mild and does not require treatment [1][7]. However, recent studies in genetically engineered murine models have revealed a potential mechanistic link between *ATRX* mutations and metabolic dysfunction [3][4][5].

Findings from murine models provide compelling evidence that *ATRX* deficiency can disrupt glucose metabolism and result in clinically significant diabetes mellitus. This case report presents a patient with ATR-X syndrome who presented with marked hyperglycemia and elevated glycosylated hemoglobin (HbA1c) consistent with diabetes mellitus, suggesting that these links in murine models may translate to human disease processes.

2. Case Presentation

The patient is a 14-year-old male with ATR-X syndrome diagnosed at 20 months of age via sequence analysis confirming a homozygous deletion (c.7301delG; p.Gly2434Valfs*4) resulting in a frameshift mutation at codon 2434 in the *ATRX* gene. This mutation was reported to be expected to result in the premature truncation of the *ATRX* gene and to have a deleterious effect on protein function. The patient has developed multiple comorbidities associated with ATR-X syndrome including severe/profound global developmental delay, microcephaly, abnormal corpus callosum, mild bilateral optic atrophy and cortical visual impairment, facial dysmorphism, alpha thalassemia (last packed red blood cell transfusion approximately 7 months prior to this presentation), scoliosis, osteoporosis, hypotonia, chronic lung disease that is tracheostomy- and oxygen-dependent, gastrointestinal reflux requiring Nissen fundoplication and gastrostomy dependance, and urogenital anomalies (inguinal hernia and undescended testes). He presented to the emergency department due to fever, lethargy, and increased, darker, and thicker tracheal secretions of three days of progression that did not respond to outpatient treatment with albuterol and hypertonic saline. He did not have oxygen desaturation and continued with his home baseline 2L oxygen requirement. He was admitted for evaluation and management of recurrent versus treatment failure of pseudomonal tracheitis needing escalation to intravenous (IV) antibiotics therapy with meropenem after completing antibiotic treatment with cefepime a week prior to the

admission. On initial presentation, laboratory evaluation revealed leukocytosis (white blood cell count 11.3 k/uL), polycythemia thought to be secondary to dehydration that included a hemoglobin level of 12.2 g/dL, hematocrit of 55.4%, mean corpuscular volume 79 fL, mean corpuscular hemoglobin 23 pg, and red cell distribution width 19.5%. He received IV hydration with normal saline due to laboratory results concerning for dehydration. While admitted, he resumed his home feeds and gastroenterology regimen of erythromycin, omeprazole, and calcium carbonate. His home feeding regimen consisted of enteral nutrition via gastrostomy tube and a scheduled regimen of Alfamino Jr. 20 calories/ounce at 105 cc/hour for a total of 18 hours per day. Initial respiratory management focused on improving airway clearance and ensuring adequate oxygenation. Ultimately, he was restarted on his home respiratory therapies with albuterol and hypertonic saline. In addition, he was started on intrapulmonary percussive ventilation and chest physiotherapy. His chronic home respiratory regimen continued, including inhaled tobramycin and budesonide, daily intranasal fluticasone, and supplemental oxygen through the tracheostomy. Patient did not require systemic steroids during this admission.

The specific concern prompting endocrine evaluation was marked hyperglycemia (random glucose level 499 mg/dL (27.72 mmol/L)). Further evaluation revealed a fasting plasma glucose of 320 mg/dL (17.65 mmol/L), an elevated HbA1c of 10.2%, and mild ketosis (beta hydroxybutyrate of 0.71 mmol/L) without acidosis (pH of 7.32). As per relatives and caregivers, the patient had polyuria, polydipsia, and unintentional weight loss of 15 pounds (7 kg) in the previous month. Family history is significant for a 20-year-old brother also with ATR-X syndrome who was diagnosed with diabetes mellitus of unknown etiology around the age of 16 years and has been insulin-dependent since then.

2.1 Diagnostic Assessment

Diagnosis of new onset diabetes mellitus was confirmed by an elevated HbA1c more than 6.5%, random glucose over 200 mg/dL (11.1 mmol/L), and a fasting glucose above 125 mg/dL (6.9 mmol/L). Type 1 diabetes mellitus (T1DM) -related autoantibodies of this patient were negative, including glutamic acid decarboxylase, islet antigen 2, zinc transporter 8, islet cell, and insulin. The C-peptide level was 1.74 ng/ml (0.57 nmol/L) (fasting reference range 0.81–3.85 ng/ml (0.28–1.27 nmol/L)). Other autoimmune labs including those for celiac disease and thyroid dysfunction were negative.

2.2 Treatment

Carbohydrate content of the formula was calculated (116g carbohydrates per feed) to guide initial prandial insulin dosing. During hospitalization, the patient was started on a physiologic subcutaneous insulin regimen at an approximate starting dose of 0.5 units/kg/day to achieve safe and controlled glycemic stabilization. The initial approach was intended to ensure alignment between insulin pharmacodynamics and the patient's predictable enteral carbohydrate intake while reducing extreme variability in blood glucose levels to prevent hyperglycemia and hypoglycemia. Basal coverage was provided with 9 unit of insulin glargine daily to ensure consistent background insulin throughout the day. Prandial insulin consisted of insulin lispro using a carbohydrate ratio of 1 unit per 25 grams of carbohydrates. The dose was adapted to the patient's continuous enteral feeding schedule and

consideration of the half-life of the insulin to provide full coverage while avoiding extended insulin that might have resulted in hypoglycemia if feedings were held. The total carbohydrate coverage was divided into two separate doses, the first administered prior to each feeding and the second provided halfway through the feeding to cover the remaining carbohydrate intake. Correctional boluses for hyperglycemia were only given in the beginning of the feeding with a correction factor of 1 unit per point-of-care glucose of 85 mg/dL (4.7 mmol/L) above 150 mg/dL (8.3mmol/L). Corrections were avoided at the midpoint to minimize hypoglycemia risk given the expected rise in blood glucose levels while on feedings.

2.3 Outcome and Follow-up

The persistence of hyperglycemia despite initiation of insulin therapy prompted a rigorous evaluation of his blood glucose patterns and insulin requirements. A continuous glucose monitor (CGM) was placed during admission and used to track glycemic trends and guide insulin adjustments. Review of the overall glycemic trends, both the total daily insulin and the patient's pre-feeding blood glucose patterns were used to guide adjustments in the regimen. Pre-feeding glucose values were incorporated to refine the basal insulin dose and the carbohydrate ratio, optimizing both background glycemic control and prandial coverage. Additionally, the total daily insulin dose provided information to adjust the basal insulin. The correction factor was reassessed based on pre- and post-feed glucose responses, allowing safe and effective correction of hyperglycemia while minimizing the risk of insulin stacking or hypoglycemia. This structured approach helped tailor the regimen to the patient's feeding schedule and metabolic needs.

Adjustments were made daily using updated glycemic data. His discharge insulin regimen consisted of 12 units of insulin glargine daily for basal coverage with 8 units of insulin lispro at the start of each feed and 10 units halfway through the feed. Additionally, a correctional sliding scale was provided to correct for hyperglycemia before feeds. The family was educated on the use of a CGM, proper technique of subcutaneous insulin administration, recognition of signs and symptoms of hypoglycemia/hyperglycemia, and management of common diabetic emergencies.

Following discharge, the patient showed progressive improvement in glycemia. Initial glucose readings on his CGM two weeks following discharge ranged from 180–350 mg/dL (10-19.5 mmol/L). Over the next three months, his average daily glucose stabilized between 110–180 mg/dL (6–10 mmol/L), with a marked reduction in hyperglycemic excursions above 250 mg/dL (13.8 mmol/L). HbA1c decreased from 10.2% at diagnosis to 7.6% at his three-month follow-up, reflecting improved glycemia. No episodes of severe hypoglycemia or diabetic ketoacidosis occurred in the time between hospital discharge and his follow-up visit. He continues to use a CGM with current insulin regimen as follows: 10 units of basal insulin glargine daily, 6 units of insulin lispro prior to meals with a correction factor sliding scale of 1 unit per glucose of 100 mg/dL (5.5 mmol/L) above 200 mg/dL (11.1 mmol/L), and an additional 8 units of insulin lispro midway through his feeds.

3. Discussion

Diabetes mellitus in children and adolescents is most often associated with autoimmune destruction of pancreatic β-cells, characteristic of T1DM. Type 2 diabetes mellitus (T2DM) in youth is increasing in prevalence but generally occurs in the context of obesity and clinical signs of insulin resistance such as acanthosis nigricans. When a patient presents with diabetes without the clinical, biochemical, or immunologic features of either T1DM or T2DM, alternative etiologies should be explored. These include monogenic forms of diabetes, syndromic disorders, and genetic conditions that impair β-cell function, insulin secretion, and/or glucose homeostasis. In this context, careful assessment of comorbidities, current medical therapy, family history, developmental features, and genetic findings is essential.

ATR-X syndrome is a rare, X-linked genetic disorder caused by pathogenic variants in the *ATRX* gene that encodes a chromatin-remodeling protein involved in transcriptional regulation, DNA methylation, and genomic stability. Clinically, ATR-X syndrome is characterized by global developmental delay or intellectual disability, hypotonia, dysmorphic facial features, and alpha-thalassemia of variable severity. Endocrine dysfunctions in ATR-X syndrome most commonly involve abnormalities of growth resulting in short stature and gonadal development that might vary from hypospadias or undescended testes to normal-appearing female external genitalia in patients with a karyotype of 46, XY [1][5][7].

Although diabetes has been reported as part of the spectrum of several conditions, including maturity-onset diabetes in the young (MODY), cystic fibrosis-related diabetes (CFRD), and mitochondrial diabetes, it is not considered a typical clinical manifestation of ATR-X syndrome in humans. This case presents a novel connection between ATR-X syndrome and diabetes mellitus in humans, though the etiopathogenesis remains unclear. Emerging evidence from murine models demonstrates an association between *ATRX* deficiency and disordered glucose regulation. Conditional knockout in mouse models has shown that *ATRX* plays a key role in endocrine organ development and metabolic homeostasis [3][4]. In these models, loss of *ATRX* function has been associated with impaired growth, pituitary hormone deficiencies, and abnormalities in pancreatic structure and function. Pancreatic findings include interlobular edema, ductal dilation, loss of lobular organization, ductal dysplasia, perivascular, peripancreatic, islet, and acinar inflammation, hyperplasia of the islet cells, and fatty infiltrates, all of which can contribute to alterations in insulin secretion [3][4]. These histopathological findings suggest that *ATRX* plays a critical role in maintaining pancreatic endocrine homeostasis and metabolic health. These structural and inflammatory changes resemble those documented in other forms of syndromic or inflammatory diabetes, including CFRD, where chronic inflammatory injury contributes to progressive β-cell dysfunction.

Further, murine studies have shown that *ATRX* disruption accelerates aging-related deterioration in endocrine tissue, particularly within pancreatic islets. These changes contribute to impaired glucose tolerance, dysregulated insulin secretion, and β-cell vulnerability to metabolic stress. Additionally, lipid infiltration of pancreatic tissue in *ATRX*-deficient mice suggests a link between *ATRX* dysfunction and metabolic dysregulation at the cellular and tissue levels. While some *ATRX*-deficient models show increased weight gain and markers of insulin resistance, impaired glucose tolerance did not correlate directly with weight, indicating that intrinsic β-cell dysfunction is likely the primary driver of dysglycemia

[3][4]. These findings support the hypothesis that diabetes in *ATRX* deficiency may result from progressive loss of endocrine competence rather than peripheral metabolic causes.

The patient's presentation with non-autoimmune diabetes supported by negative islet autoantibodies that would support a diagnosis of T1DM and without physical findings suggestive of insulin resistance with an inappropriately normal C-peptide for the degree of hyperglycemia and a total daily dose of only 0.6 u/kg/day non-suggestive of T2DM (which requires up to 1 u/kg/day) underscores the importance of considering diabetes secondary to uncommon etiologies. The presence of diabetes mellitus in two siblings with genetically confirmed ATR-X syndrome that were diagnosed at similar ages and in the absence of autoimmunity or insulin resistance strongly suggests a potential syndromic association and the potential need for consideration of glycemic monitoring in this population.

Because of this potential connection, it is reasonable to evaluate diabetes as a feature of ATR-X syndrome, considering the presentation of diabetes in these two young patients and the significant endocrine disturbances seen in *ATRX*-deficient mice, including the development of increased body weight, impaired glucose tolerance, and overt diabetes mellitus phenotypes. The possible link between *ATRX* dysfunction and dysglycemia supports the need for screening strategies which should start with a thorough history and examination that specifically assess for signs and symptoms of dysglycemia, as well as risk factors that could possibly alert for earlier screening. Given the age of presentation of these patients during their teen years, laboratory evaluation such as fasting or random glucose, oral glucose tolerance testing, and/or HbA1c should be considered as part of the routine screening for comorbidities associated with ATR-X syndrome.

Failure to recognize or routinely screen for diabetes may lead to progressive hyperglycemia, delayed initiation of appropriate therapy, and an increased risk for both acute metabolic decompensation and long-term microvascular/macrovascular complications, all of which may further worsen the already fragile baseline medical status in these patients. It is essential to acknowledge that HbA1c may be falsely low in patients with α-thalassemia due to altered red blood cell turnover and hemoglobin fractionation. Therefore, oral glucose tolerance testing may be more ideal as the initial test for early detection and surveillance in patients with ATR-X syndrome. Diagnosis and management of diabetes mellitus can impose a significant medical, economical, and psychological load for patient and caregivers. Early diagnosis helps alleviate this burden making it crucial to consider the screening of diabetes as part of the routine evaluation of these patients to allow the use of broader therapeutic strategies and provides an opportunity to prevent or delay long-term complications in an already medically complex patient population.

4. Take-away Points

1. This case expands the endocrine phenotype associated with ATR-X syndrome by highlighting the potential development of dysglycemia and ultimately diabetes mellitus.

2. Findings from *ATRX*-deficient murine models provide biologic plausibility of inherent diabetes risk by demonstrating β-cell dysfunction, inflammatory infiltration, and metabolic impairment.
3. Recognition of diabetes as a possible manifestation of ATR-X syndrome supports the need for multidisciplinary management and careful genetic counseling.
4. Further research and additional clinical reports will be essential to determine whether diabetes mellitus should be incorporated into the recognized ATR-X clinical spectrum.

Declarations

Informed Patient Consent for Publication

Informed consent obtained directly from the patient's relatives or guardians.

Conflict of Interest

The authors declare that the case was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

All authors made individual contributions to the conception and design of the case report. C.P.M and A.K. performed the literature review. All authors were involved in the diagnosis and management of this patient. C.P.M. drafted the initial manuscript. All authors critically reviewed and revised the manuscript for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work.

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