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Case Report

Internal Medicine Section

Neuro-reproductive Malformations and Hypogonadism in a Young Adult with Type 1 Diabetes: A Case Report of Partial Dysgenesis of the Corpus Callosum

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ABSTRACT

The coexistence of partial dysgenesis of the corpus callosum, reproductive tract anomalies, and endocrine disorders in the patient presents unique diagnostic and management challenges. This case report contributes to the limited literature on complex multisystem presentations that require coordinated multidisciplinary care. This case is about a phenotypically female patient who presented to the Department of General Medicine with chief complaints of poorly controlled Type 1 Diabetes Mellitus (diagnosed eight years ago) and acute systemic symptoms, which included fever, non-bilious vomiting (2-3 episodes), decreased appetite for three days, and a history of primary amenorrhoea that had never been previously evaluated. Patient's vitals were normal except for a temperature of 101°F. Physical examination revealed dysmorphic facies, with hypertelorism, rudimentary breast, a left-sided unilateral complete cleft lip and a unilateral cleft palate. Neurological assessment indicated global developmental delay with a clinically estimated IQ of 70, while bedside olfactory testing with standard odours (coffee, peppermint) confirmed normal olfaction. A detailed genital examination revealed a normal vaginal canal. Pelvic ultrasonography identified a rudimentary uterus. Neuroimaging demonstrated partial corpus callosum dysgenesis, in which the rostrum, genu, and body were not seen. The patient responded favourably to supportive care, including intravenous fluids, antiemetics, empiric antibiotics, and a basal-bolus insulin regimen, achieving clinical improvement. Genetic testing was initiated to evaluate this complex presentation comprehensively. The patient's chromosomes were 46, XX. The patient was then referred to higher centres for hormone replacement therapy. This case underscores the necessity of investigating "silent" neurological and reproductive anomalies in adolescents with uncontrolled metabolic disease and developmental delay. It highlights a multidisciplinary approach involving endocrinology, neurology, and gynaecology to address the multifaceted health needs of these patients.

Keywords: Amenorrhoea, Cleft lip, Hypertelorism, Mayer-rokitansky-küster-hauser syndrome, Medicine, Radiology

CASE REPORT

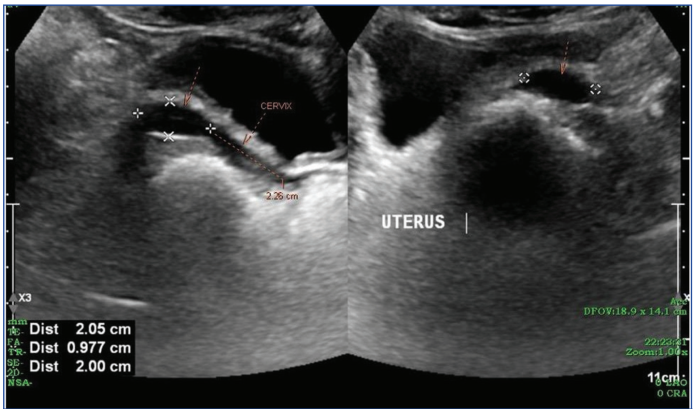
A phenotypically female 26-year-old patient presented to the Department of General Medicine with chief complaints of fever, non-bilious vomiting (2-3 episodes), decreased appetite for three days, and a history of amenorrhoea. The patient's fever was insidious in onset, continuous, and relieved on medication. The patient had a history of type 1 diabetes mellitus (diagnosed 8 years ago) on irregular treatment with a random blood sugar of 245 mg/dL. The patient's relative gave a history that the patient never had menstruation before, and it had also never been evaluated for the same, i.e., primary amenorrhoea. Family history was not significant, with no consanguineous marriages or diabetes. The patient cried immediately after the birth.

The patient was admitted to the medicine ward. On admission, the patient's vitals were stable, except for a higher body temperature of 101°F; general examination revealed developmental delay and a low Intellectual Quotient (IQ). Global developmental delay was retrospectively established based on a detailed parental history of delayed milestones, including the patient not walking until age three and delayed speech acquisition. The patient's IQ was formally assessed by the department of paediatrics using the Wechsler Adult Intelligence Scale, yielding an IQ of 70 [1]. The patient also had hypertelorism facies, a left-sided unilateral complete cleft lip, and a complete cleft palate involving both the hard and soft palate. No anosmia was detected by bedside olfactory testing with standard odours (coffee, peppermint), effectively ruling out anosmia. Visual acuity and fields were clinically normal, extraocular movements were full without nystagmus, and pupillary reflexes were preserved. There were no signs of facial asymmetry, hearing loss, or lower cranial nerve palsies. Motor system examination showed normal muscle bulk, tone, and Grade 5/5 power in all extremities. Sensory modalities, including crude touch, pain, temperature, vibration, and proprioception, were intact bilaterally. Deep tendon reflexes were normal with bilateral flexor plantar responses. Cerebellar signs were absent, and there were no signs of meningeal irritation. Sexual Maturity Rating (SMR) was consistent with Tanner Stage II for breast development. Other systemic examination findings were normal. An obstetrics and gynaecology opinion was obtained to rule out anatomical defects, such as an imperforate hymen and cryptomenorrhea. A detailed genital examination revealed normal external genitalia. Laboratory studies showed severely elevated HbA1c of 10.6% (reference range: 4.0-5.9%) and average estimated glucose of 257.5 mg/dL (reference range: 90-120 mg/dL). Other laboratory levels included a normal advanced thyroid profile, FSH, and LH, with estrogen levels below those of normal men. Karyotyping was performed using G-banding (Giemsa staining), which was suggestive of a 46, XX karyotype. Initial laboratory investigations were shown in [Table/Fig-1].

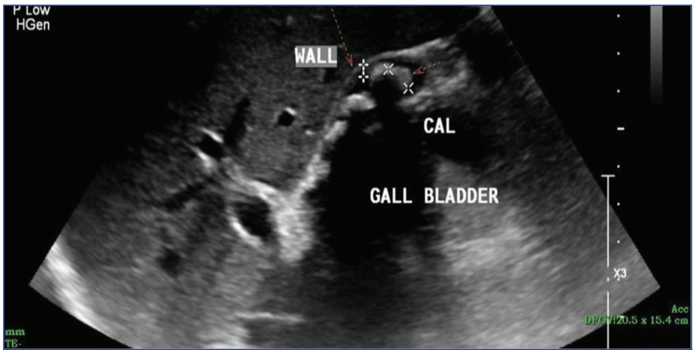
Pelvic ultrasound revealed rudimentary uterine development suggesting possible Mullerian agenesis or Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome requiring further reproductive endocrine evaluation. Abdominal ultrasound: Demonstrated a well-distended gallbladder with normal wall thickness, containing multiple intraluminal calculi, an incidental finding [Table/Fig-2,3]. Brain MRI-demonstrated non-visualisation of the corpus callosum's rostrum, genu, and body, accompanied by widely spaced, parallel lateral

Parameter	Patient value	Reference range
Haemoglobin A1c (HbA1c)	10.6%	4.0 - 5.9%
Random blood glucose (admission)	257.5 mg/dL	< 140 mg/dL
Fasting blood glucose (day 2)	145 mg/dL	70 - 100 mg/dL
Follicle Stimulating Hormone (FSH)	0.300	3.5 - 12.5 mIU/mL
Luteinising Hormone (LH)	0.100	2.4 - 12.6 mIU/mL
Oestrogen (E2)	83.263 pg/mL	30 to 400 pg/mL
Thyroid Stimulating Hormone (TSH)	2.4 μIU/mL	0.4 - 4.0 μIU/mL
Karyotype	46, XX	46, XX
Serum prolactin	3.92 ng/mL	(4.1 - 28.9) ng/mL

[Table/Fig-1]: Laboratory investigations of the patient.

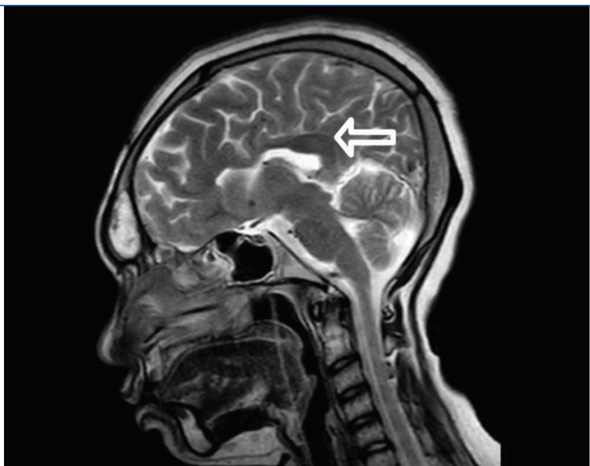


[Table/Fig-2]: Sagittal and transverse transabdominal ultrasound images showing an atrophic uterus. A hypoplastic uterus with a uterine body (2.0 cm) and an elongated cervix (2.2 cm), resulting in an abnormal uterocervical ratio for this age.



[Table/Fig-3]: Transabdominal ultrasound shows a well-distended gall bladder with normal wall thickness containing a few intraluminal calculi with associated posterior acoustic shadowing.

ventricles and narrow frontal horns [Table/Fig-4]. These findings were diagnostic of partial corpus callosum dysgenesis, a significant congenital neuroanatomical anomaly.



[Table/Fig-4]: Sagittal T2-weighted MRI of the brain showing partial corpus callosum dysgenesis in the form of non-visualisation of body and isthmus, partly visualised rostrum and genu, with an appearing splenium of corpus callosum with normal pituitary.

Treatment in this patient included maintenance of fluid and electrolyte balance, adequate nutritional support, and monitoring of vital signs, neurological status, and glycaemic control throughout the hospital. Treatment was initiated, including syrup sucralfate 5 mL thrice daily, half an hour before meals, and injection ceftriaxone 1 gm twice daily after food. Blood glucose levels were successfully stabilised through optimal insulin management. Regular insulin (6 international units subcutaneously, given one hour before meals three times), a long-acting insulin (12 units once a day at night), and other supportive measures. During the initial treatment of the patient, the patient's condition drastically improved, which included complete resolution of the fever and vomiting within two days. Patient improved symptomatically with no adverse effects and was discharged in haemodynamically stable condition, with a pulse rate of 78 beats per minute, blood pressure of 112/70 mmHg, and temperature of 97.5 degrees Fahrenheit. The patient was advised to follow-up after seven days with a fasting blood sugar test. The patient was also referred to higher centres in the department of endocrinology to start hormonal replacement therapy. The patient was given advice and asked to come for a follow-up, but they chose not to do so.

DISCUSSION

Partial dysgenesis of the corpus callosum is one of the rarest brain malformations in humans, with an incidence of 0.5-70 per 10,000 births [2]. While many isolated cases remain asymptomatic throughout life, the association with reproductive tract abnormalities and endocrine disorders raises suspicion of syndromic presentations requiring comprehensive genetic evaluation and management. The MRKH syndrome, affecting approximately 1 in 4,500-5,000 female births, is characterised by congenital absence or underdevelopment of the uterus and upper vagina [3]. The approach to this patient was done as the authors first evaluated the causes of primary amenorrhoea. Following the clinical and sonographic findings of an atrophic uterus with low FSH values, a differential diagnosis of Kallmann syndrome, Sheehan syndrome, and anorexia nervosa was initially considered. Kallmann syndrome was excluded because anosmia was absent on formal olfactory testing. Sheehan syndrome was deemed unlikely given the patient's nulliparous status and lack of obstetric haemorrhage, while anorexia nervosa was ruled out based on clinical history. Other differential diagnoses included disorders of Müllerian development. Müllerian agenesis, specifically MRKH syndrome, was considered in view of the 46, XX karyotype demonstrated by G-banding (Giemsa staining) and the presence of a rudimentary uterus rather than complete uterine absence. However, the coexistence of partial corpus callosum dysgenesis suggested a broader syndromic aetiology rather than isolated MRKH syndrome [4]. Other differential diagnoses include true gonadal dysgenesis, but in our case, the FSH levels were not increased. And on top of all that, none of the above diseases exists with partial corpus callosal dysgenesis.

However, recent genomic literature suggests that the simultaneous presentation of Type 1 Diabetes, Müllerian agenesis, and dysgenesis of the corpus callosum may not be coincidental but rather the manifestation of a contiguous gene syndrome, most notably the 17q12 deletion syndrome [5]. This chromosomal region houses two critical transcription factors: HNF1B and LHX1. HNF1B mutations are responsible for Maturity-Onset Diabetes of the Young type 5 (MODY5), a condition frequently misdiagnosed as Type 1 diabetes in adolescents due to the requirement for insulin therapy, yet distinct due to the absence of autoantibodies and the frequent association with genitourinary malformations and liver dysfunction (noted here as cholelithiasis) [6]. Concurrently, the LHX1 gene, located adjacent to HNF1B, is essential for the development of the intermediate mesoderm into the reproductive tract; its haploinsufficiency has been directly linked to MRKH syndrome. Crucially, recent neurodevelopmental studies have shown that LHX1 is also expressed in the anterior neural plate and is required for the guidance of midline-crossing commissural axons; thus, its loss provides a specific embryological mechanism to explain the partial dysgenesis of the corpus callosum observed in this patient [7,8]. This rare triad of endocrine, reproductive, and neurological deficits strongly supports a diagnosis of a 17q12 microdeletion, necessitating a shift in management to include renal surveillance and genetic counseling for potential MODY5 rather than classic autoimmune diabetes [9].

The constellation of partially dysgenetic corpus callosum, rudimentary uterus, and type I diabetes mellitus represents a unique presentation, with limited medical literature availability. Partial dysgenesis of the corpus callosum can occur in isolation or as a part of a syndromic presentation with associated anomalies reported in 39.6% to 86.5% of cases at birth [10]. MRKH syndrome affects reproductive tract development during embryogenesis and is classified into type I (Isolated) and type II (with associated anomalies). Type II contributes to approximately 43.5% of cases [11]. Type I diabetes mellitus in adolescent individuals presents typical management challenges due to increasing insulin resistance by 30-50% during puberty, thereby disrupting glycaemic control, which can cause growth failure and retard pubertal progression also [12]. The multidisciplinary model used in this case is supported by the current evidence-based literature for managing complex disorders in such age groups.

CONCLUSION(S)

This case report is presented to highlight the diagnostic and therapeutic challenges encountered in a patient with an unusual constellation of findings. The authors emphasise that the clinical presentation extends beyond what is currently described in the literature and underscore the importance of incorporating neurological evaluation in cases of primary amenorrhoea, a consideration frequently overlooked in routine practice. To the best of current knowledge, this may represent the first reported case describing the co-existence of partial corpus callosum agenesis, primary amenorrhoea with abnormal laboratory parameters, a uterine anomaly, and Type 1 diabetes mellitus.

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