A Tale of Three CTs: A Hip Fracture in a Patient with Down Syndrome Uncovers an Endocrinologic Iceberg

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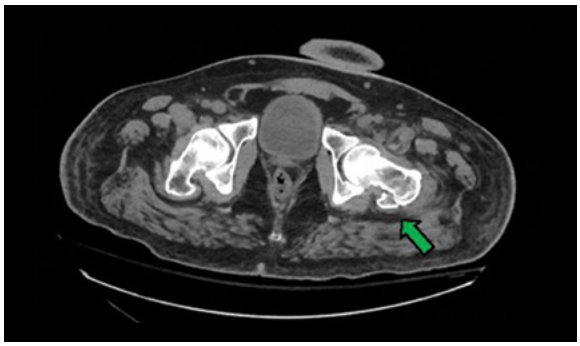
PATIENT DESCRIPTION

A 32-year-old man with Down syndrome (DS), nonverbal due to severe cognitive impairment, presented to the emergency department after sustaining a fall from standing, causing trauma to his left hip. He had no known chronic medication use. His previous medical history included hospitalizations for severe COVID-2019 in 2021 and herpes simplex virus stomatitis in 2017. Following the fall, he was unable to bear weight on the affected limb. On physical examination, his left leg was externally rotated with preserved neurovascular status. Given the mechanism of injury and clinical presentation, non-contrast computed tomography (NCCT) was obtained to assess fractures and underlying pathology [Figure 1A].

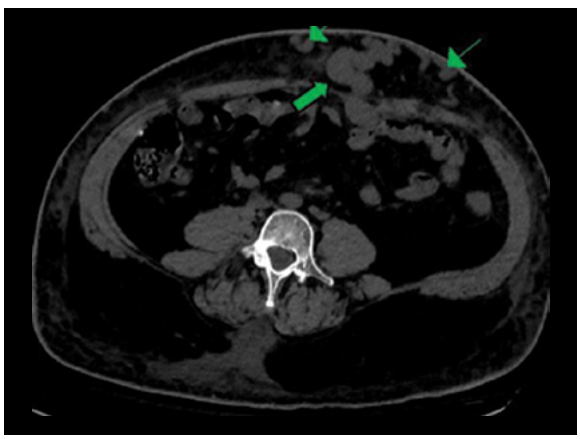
The imaging revealed a left intertrochanteric femoral fracture with varus angulation of the fracture fragments (AO classification 31A2). The hip joint alignment was preserved, with no evidence of significant joint

Figure 1. Axial non-contrast CT images

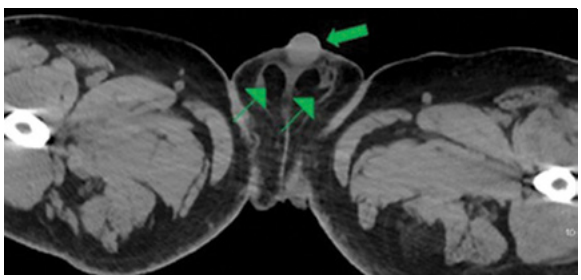
CT = computed tomography



[A] Pelvis showing left intertrochanteric femoral fraction (arrow)



[B] Abdomen showing periumbilical varices (arrowheads) with a recanalized paraumbilical vein (arrow)



[C] Pelvis revealing atrophic testicles (arrowheads) and reduced penile size (arrow)

effusion. Notable soft tissue changes included swelling and infiltration of the adjacent fat and musculature. Meanwhile, initial labs revealed bicytopenia, with hemoglobin of 6.57 g/dl and a platelet count of 75 × 10^9/L. Based on these findings, the patient was admitted to an internal medicine ward for stabilization prior to surgery. An anemia workup was conducted to investigate potential underlying causes. The mean corpuscular volume was 80 fl, and the reticulocyte index was 0.4, indicating a hypoproliferative anemia. Further testing revealed severe iron deficiency, with a transferrin saturation of 5% and a low ferritin level of 11 ng/ml. Vitamin B12 and folic acid levels were within normal limits. Concurrent biochemical abnormalities, including hypoalbuminemia (2.4 g/dl) and a prolonged INR of 1.88, suggested impaired synthetic liver function. Other than significant central obesity, the abdominal examination was normal, with no overt abdominal wall edema or significant ascites. These findings warranted a second look at the original NCCT [Figure 1B].

At the upper border of the imaging field, prominent periumbilical varices were observed, accompanied by subcutaneous fat edema. In addition, a small ventral abdominal wall hernia was present, which contained a recanalized and enlarged paraumbilical vein. Thus, a diagnosis of cirrhosis was confirmed, corroborated by an abdominal ultrasound that demonstrated a lobular and heterogenous liver and splenomegaly, findings that are consistent with portal hypertension secondary to liver cirrhosis.

A comprehensive evaluation was conducted to determine the etiology of the patient's cirrhosis. Viral hepatitis screening was negative for hepatitis. Celiac screening was also negative. Autoimmune hepatitis was considered, with serologic testing revealing positive antinuclear antibodies (1:160) and elevated anti-actin antibodies (33, reference range 1–20), while smooth muscle antibody was borderline. Hemochromatosis was deemed improbable due to longstanding evidence of low ferritin and iron saturation. Wilson's disease was considered unlikely because of normal 24-hour urinary copper excretion. Alpha-1 antitrypsin levels were normal. As metabolic dysfunction-associated steatotic liver disease (MASLD) is strongly linked to DS, this etiology was presumed and a liver biopsy was waived [1]. While the lack of histological confirmation limits diagnostic certainty, the patient's frail baseline status and the presence of advanced liver disease led the clinical team to conclude that the risks of biopsy outweighed its potential utility.

After 5 days of hospitalization in the internal medicine ward, during which hematologic stabilization was achieved and anesthesia evaluation was obtained, the patient underwent closed reduction and internal fixation of the fracture using an intramedullary nail. The result was satisfactory, both radiographically and clinically, with no leg length discrepancy or abnormal femoral rotation. The patient was allowed weight-bearing as tolerated, and physiotherapy was initiated on postoperative day one.

Notably, neither DS nor cirrhosis are sufficient to explain an osteoporotic fracture in a young man. Thus, a differential diagnosis for osteoporosis was conducted, and a third look at the original NCCT was made [Figure 1C]. Although ultrasound is the modality of choice for testicular evaluation, the testes are partially visualized in this CT. Both testes appeared reduced in size, compatible with testicular atrophy. An extensive endocrine evaluation was performed, which suggested hypogonadism as a possible underlying cause for osteoporosis. The results revealed unmeasurable levels of FSH and LH (< 1 IU/L), and a low testosterone level of 3.7 nmol/L (reference range 8–29 nmol/L). This hormonal pattern is more consistent with central (hypogonadotropic) hypogonadism rather than primary testicular failure, in which gonadotropin levels would typically be elevated due to reduced negative feedback. Other endocrine axes were assessed with the following results: prolactin 21.6 mcg/l (4.04–15.2), progesterone unmeasurable, 17B-estradiol 476 pmol/l (41.4–159), ACTH 47.1 pg/ml (7.2–63.6), cortisol 249 nmol/l (172–497), and growth hormone 1.8 mcg/l (0–2.47). Prolactin is frequently elevated in cirrhotic patients; 17B-estradiol is frequently increased in cirrhotic and obese patients. The remaining endocrine axes were within normal limits.

The patient's family and medical records denied the use of gonadotropin-releasing hormone (GnRH) agonists, historically used for castration of mentally impaired individuals. Findings were consistent with a diagnosis of solitary central hypogonadism, although no underlying cause could be identified, including in a subsequent head CT.

COMMENT

CIRRHOSIS IN DOWN SYNDROME

DS is strongly associated with MASLD. Valentini and colleagues [1] found that MASLD affected 45% of nonobese and 82% of overweight/

obese children with DS, compared to 5.7% and 33%, respectively, in European nonobese and obese pediatric populations. This difference suggests that DS is associated with an intrinsic susceptibility to MASLD, beyond the effects of excess weight alone. This finding may be partly explained by characteristic features of DS, including a lower resting metabolic rate, reduced physical activity, and increased consumption of energy-dense, nutrient-poor foods [1].

In addition to the increased risk for metabolic disorders, DS is also characterized by higher susceptibility to autoimmune diseases [2]. In our case, the cirrhosis workup revealed several characteristics that might suggest the possibility of autoimmune hepatitis, such as hypergammaglobulinemia and elevated titer of anti-actin and anti-nuclear antibodies. Nevertheless, these findings were not diagnostic, as they could also align with polyclonal hypergammaglobulinemia, a common feature observed in various forms of cirrhosis. Given the overlap of these clinical and laboratory findings, a definitive diagnosis would require a liver biopsy for further investigation. Celiac disease may also lead to cirrhosis and iron deficiency anemia like our patient had but was sufficiently ruled out with negative serologies (namely anti-tissue transglutaminase, anti-endomysial antibody).

HYPOGONADISM IN DOWN SYNDROME

To the best of our knowledge, there is no well-established association between DS and central hypogonadism in males [3]. In our case, central hypogonadism was identified, as evident by low levels of FSH and LH, pointing to a potential pituitary or hypothalamic dysfunction. A pituitary abnormality is less likely given the isolated sex hormone deficiency and the preservation of other hypothalamic-pituitary-adrenal axis functions. Although use of GnRH agonists for behavioral castration was raised as a differential diagnosis, parental questioning denied this possibility. Considering the combination of cirrhosis and central hypogonadism, hemochromatosis was also considered, but this diagnosis appears unlikely. Anemia workup from 2017 to 2024 revealed low ferritin and transferrin saturation, both of which are typically elevated in classic hemochromatosis. In addition, hemochromatosis usually presents between ages 40 and 60 years and rarely before the age of 20 years, whereas the patient was genitally pre-pubertal [4]. There is no known association between DS and hemochromatosis. Full evaluation of central hypogonadism entails a GnRH stimulation test and a brain magnetic resonance imaging (MRI), both of which were waived in this case.

OSTEOPOROSIS IN DOWN SYNDROME

Even though research demonstrates that people with DS have lower bone mineral density compared to the healthy population, we assume that given the patient's young age, osteoporosis cannot be attributed solely to DS and is most likely secondary to hypogonadism [5].

International guidelines for osteoporosis screening in individuals with DS are not well-established due to limited evidence. However, the Global Down Syndrome Foundation recommends that adults with DS who experience fragility fractures should be assessed for secondary causes of osteoporosis, including thyroid dysfunction, celiac disease, vitamin D deficiency, and medication-related bone loss (e.g., anti-convulsants). Given the high prevalence of these risk factors in DS, early identification and management are crucial to prevent further bone loss and fractures. Although routine bone density screening is not explicitly recommended, clinicians should adopt a proactive approach by encouraging weight-bearing exercises, ensuring adequate calcium and vitamin D intake, and considering individualized fracture risk assessments. In addition, shared decision-making between healthcare providers and caregivers is essential, as standard osteoporosis screening tools may not fully capture fracture risk in this population.

LIMITATIONS

Our findings have several limitations. First, the diagnosis of MASLD was made clinically, without histological confirmation via liver biopsy. Although the presumed etiology was strongly supported by the clinical context and the known association with DS, the absence of biopsy weakens diagnostic certainty. Given the patient's poor general condition and advanced liver disease, the potential risks of biopsy were considered to outweigh the expected diagnostic yield.

Second, while laboratory findings were consistent with central hypogonadism, further diagnostic workup, including pituitary imaging and dynamic hormonal testing, were not performed. Completing an MRI would have required general anesthesia due to the patient's limited cooperation, which was deemed to be an excessive risk in this context. These limitations restricted the ability to fully characterize the underlying endocrine pathology.

FOLLOW-UP

Five months after the initial hospital-

ization, the patient was re-admitted to the internal medicine ward due to anasarca with worsening abdominal and peripheral edema. A point-of-care ultrasound demonstrated ascites, although insufficient for paracentesis. Treatment with spironolactone and furosemide was initiated and follow-up was arranged with both the hepatology and endocrinology outpatient clinics. Unfortunately, the patient was lost to follow-up.

CONCLUSIONS

We present the case of a 32-year-old male with DS and a traumatic femoral fracture. An in-hospital workup revealed an endocrinological iceberg: a diagnosis of cirrhosis likely due to MASLD, central hypogonadism of unclear etiology, and early-onset osteoporosis, most probably driven by longstanding hypogonadism. This case highlights the need for comprehensive metabolic and endocrine evaluations in individuals with DS to enable early intervention and prevent complications. The patient was advised to complete further evaluation, start hormone replacement therapy for hypogonadism and anti-resorptive therapy for osteoporosis, in addition to routine monitoring for cirrhosis-related complications. We recommend considering similar screenings and interventions for the young DS population, including abdominal ultrasound for MASLD,-bone mineral density screening, and pubertal development assessment. Lifestyle modifications should also be advised to reduce long-term health risks. As most people with DS now reach late-adulthood and have a good quality of life, their preventive medicine efforts should be appropriately tailored.

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Capsule

Tissue-specific clonal selection and differentiation of CD4⁺ T cells during infection

Parsa et al. revealed that CD4⁺ T cell clonal selection and differentiation are strongly shaped by tissue-specific microenvironments during infection. Identical T cell clones were shown to adopt distinct phenotypes and effector functions depending on their anatomical location. Local antigen presentation, cytokine milieu, and stromal signals collectively influenced lineage commitment, persistence, and memory formation. The findings challenge the notion of uniform systemic T cell responses and instead support a model of regionally specialized immunity. These insights have important implications for vaccine design and for therapies targeting tissue-specific immune responses.

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Capsule

Bacteria on steroids

Men are more susceptible to skin infections than women are. Most of these infections are caused by *Staphylococcus aureus* bacteria, which only become virulent and invade the deep skin when they are sufficiently abundant. *S. aureus* bacteria communicate with each other through chemical signals to coordinate infection in a process known as quorum sensing. **John** and colleagues found that genetically engineered male mice secrete less testosterone at the skin surface were more resistant to skin infection by methicillin-resistant *S. aureus* (MRSA). Furthermore, testosterone independently activated the accessory gene regulator (*agr*) quorum-sensing pathway. A synthetic molecule that is the mirror image of testosterone inhibited *S. aureus* quorum sensing in mice and may be a potential therapy to manage skin infections.

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