

# Case Report: When an Induced Illness Looks Like a Rare Disease

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The recognition of fabricated illness (FI) in a child represents a diagnostic challenge. The suspicion of FI often arises from the discrepancy between laboratory tests and clinical history. For instance, (unnecessary) insulin injections by caregivers has been widely described as a common cause of factitious hypoglycemia that may be inferred from discrepancies between plasma insulin and c-peptide. However, contemporary administration of insulin with an insulin secretagogue (glyburide), and of additional drugs, can make the diagnostic pathway problematic. We report the case of a child 4 years and 11 months old, admitted for alternance of hypo- and hyperglycemia associated with hirsutism, hypokalemia, nephrocalcinosis, and neurodevelopmental delay. All these features were compatible with Rabson-Mendenhall syndrome, a rare disorder of severe insulin resistance linked to mutations of insulin receptor. At admission, plasma insulin levels were high during hypoglycemic episodes, but c-peptide was repeatedly in the normal range. The genetic analysis of insulin receptor was negative. The story of previous hospital admissions, inconsistency between insulin and c-peptide values, and association between hypoglycemic episodes in the child with the presence of the mother, raised the suspicion of FI. This hypothesis was confirmed by a video recording that revealed the administration by the mother of multiple drugs (insulin, glyburide, progesterone, and furosemide) that mimicked most of the features of Rabson-Mendenhall syndrome, including hirsutism and hypoglycemia with coincident, inappropriately normal c-peptide values due to the administration of the insulin secretagogue. Our case indicates that inconsistency among consecutive diagnostic tests should be regarded as a clue of FI.

One of the most challenging situations for a pediatrician is to recognize a “fabricated or induced illness in a child” (previously known as Munchausen syndrome by proxy),<sup>1</sup> especially if it closely resembles a well-defined disease or syndrome. The diagnostic delay determines a prolonged perpetration of the child’s injury and an extensive use of diagnostic, often invasive, tests to rule out a long series of possible medical diagnosis.<sup>2</sup> The clue for identification of fabricated illness (FI) is often the discrepancy between a complex

medical history (with frequent hospitalization for different symptoms) and physical signs and/or laboratory results along with poor response to the treatment. In addition, children involved in FI are often already affected by physical and/or mental disorders.<sup>1</sup> The key diagnostic criterion for factitious disorder imposed on another<sup>3</sup> is the detection of deception that is, most of the time, difficult to be demonstrated.

The case we present here came to our attention with clinical (alternance of hyper- and hypoglycemia) and

## abstract

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laboratory (high insulin levels) features resembling a severe insulin resistance syndrome.<sup>4,5</sup>

Hypoglycemia induced by the factitious injection of insulin is usually recognized from the mismatch between plasma insulin and c-peptide. However, we were confronted with the confounding effect of the administration of multiple drugs, including an insulin secretagogue (glyburide) that spuriously increased c-peptide values and made the diagnosis of FI extremely difficult.

### CASE PRESENTATION

A boy of 4 years and 11 months came to our attention for multiple

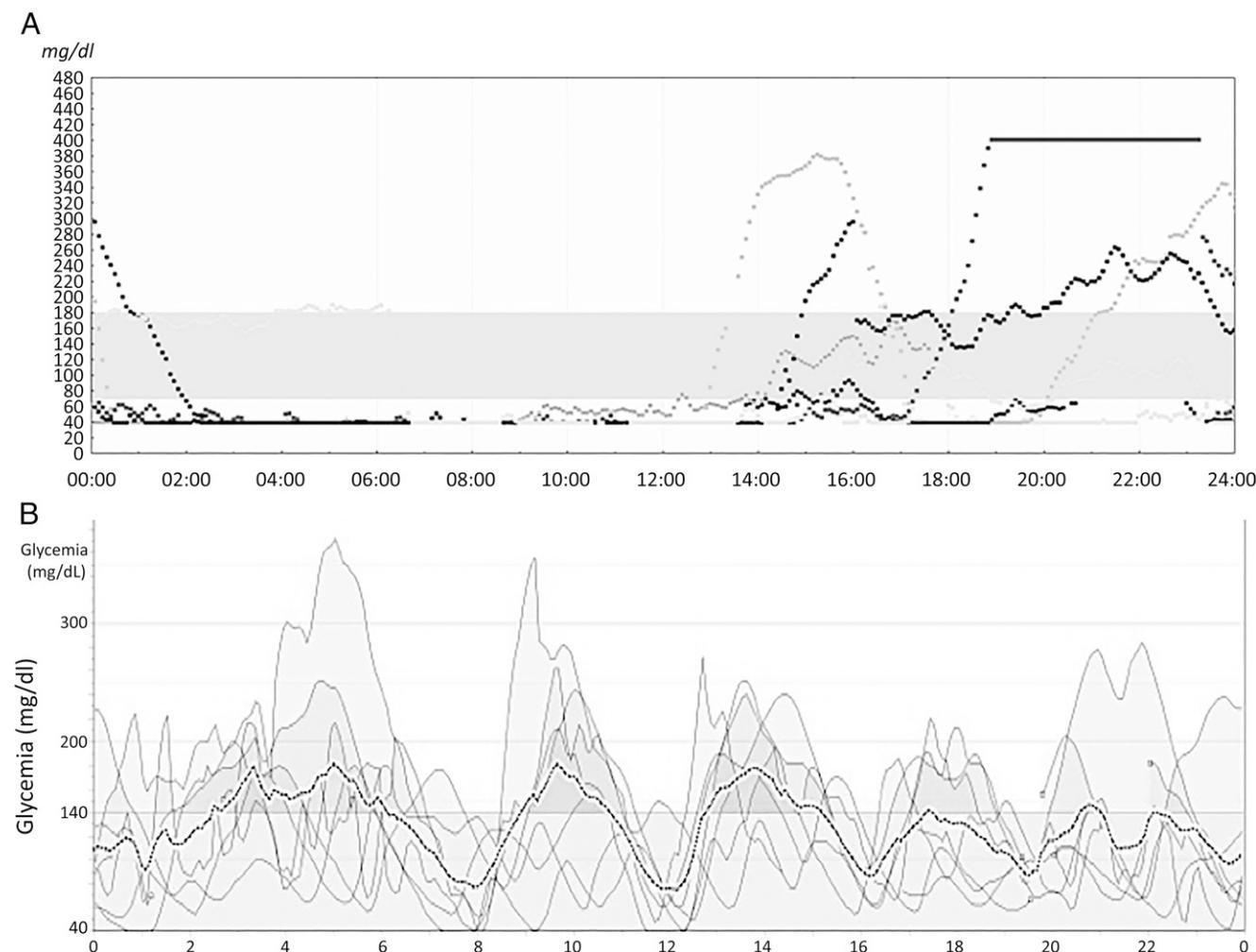
hypoglycemic episodes (<2.8 mmol/L or 50 mg/dL) during a hospitalization for gastroenteritis. It was the third admission for diarrhea, following a series of hospitalizations in other centers over preceding years for persistent (>7 days) diarrhea in the absence of an infective cause.

Among tests previously performed, there were transglutaminase autoantibodies (negative), allergy screening to rule out milk allergy (negative), and an upper endoscopy that resulted normal. Stool culture, liver function tests, pancreatic enzymes, and hematologic profile were within normal range.

The past medical history of the child was relevant for a neurodevelopment delay consequent to neonatal

ischemia, and documented generalized epilepsy poorly controlled with incremental doses of valproate (up to 60 mg/kg per day). His only caregiver was the mother, a nurse.

At our first clinical evaluation, he exhibited hirsutism (hair growth at face, dorsum, forearms, legs, upper back). Hypoglycemic episodes were confirmed in several consecutive plasma glucose determinations and prompted us to use a continuous glucose monitoring system (CGMS) (Dexcom G4 Platinum, Dexcom Inc, USA, San Diego, CA). CGMS showed an alternance of hypoglycemic events with postabsorptive hyperglycemia (up to 22.2 mmol/L) with an area under the curve <2.22 mmol/L of



**FIGURE 1**

A, Glucose values during the second week of CGMS. The wide fluctuations resemble the trend observed in a patient with RMS (B) at onset.<sup>5</sup>

50% and an area under the curve >10 mmol/L of 12% (Fig 1A). This CGMS pattern was similar to that obtained in a Rabson-Mendenhall syndrome (RMS) case with biallelic insulin receptor (*INSR*) mutations (E238K/E1074Q)<sup>5</sup> showing marked hypoglycemic episodes alternating with hyperglycemia (Fig 1B). Plasma insulin values determined during severe hypoglycemic episodes were always very high, but results of simultaneous c-peptide tests were somehow inconsistent with insulin hypersecretion (Table 1).

To avoid hypoglycemia and maintain plasma glucose >2.8 mmol/L, the patient received an infusion of 3 to 5 mg/kg per minute of glucose daily; hyperglycemic spikes were not treated because they were very short-lived. In addition, multiple blood gas analysis demonstrated metabolic alkalosis (pH 7.39–7.57, HCO<sub>3</sub> 24.7–36.1 mmol/L, pCO<sub>2</sub> 31.8–44 mm Hg, BE 3–10) with hypokalemia (1.63–4.4 mEq/L), despite a potassium supplementation of 4 mmol/kg per day, and normal serum magnesium. Thereafter, nephrocalcinosis was detected at the abdominal ultrasound (Fig 2).

During hospitalization, the patient developed 2 episodes of sepsis with high fever (>40°C) and prostration, with positive blood culture for *Escherichia coli* and for *Klebsiella spp* that responded to antibiotic therapy. However, the source of infection was not identified.

Because the association of (1) hypoglycemic hyperinsulinism with postabsorptive hyperglycemic spikes, (2) hirsutism, and (3) nephrocalcinosis was suggestive of an insulin receptoropathy,<sup>4,5</sup> the entire coding sequence of the *INSR* gene was screened, but no mutation was identified. Once we had excluded *INSR* defects, we retested the patient, but again c-peptide was detectable (ie, not suppressed during profound hypoglycemia), a result not easily reconcilable with the idea of factitious

**TABLE 1** Laboratory Results During Hypoglycemia

	Sample 1	Sample 2	Sample 3	Sample 4
Plasma insulin, $\mu\text{U/mL}$	83.6	974	306.8	104.1
Plasma glucose, mmol/L	1.0	1.4	0.8	1.16
C-peptide, nmol/L	0.4	0.25	0.29	0.57
Progesterone, nmol/L (reference values for male individuals: 0.64–4.45 nmol/L)	N/A	17.2	1	1

N/A, not available.

insulin administration. However, because of the persisting inconsistency of laboratory tests (Table 1), the patient's medical history of multiple hospitalizations, the difficult familiar background, and the suspicious coincidence of the patient's hypoglycemic crisis with the presence of the mother in the hospital ward, we considered the possibility of FI.

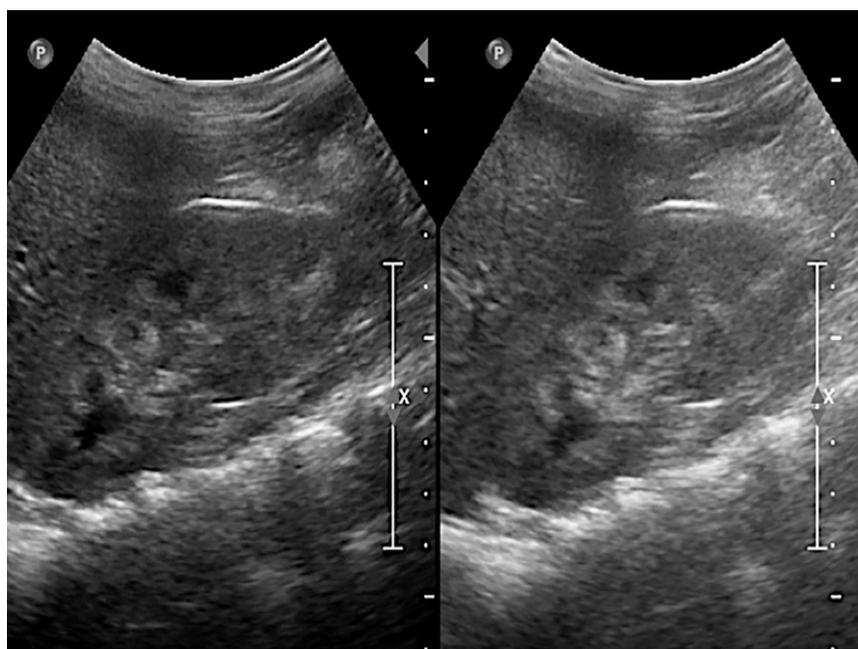
To demonstrate our suspicion, we obtained the authorization to use covert video surveillance from the Juvenile Court. Covert video surveillance captured images showing the mother while administering a number of substances to her son via different routes. After confrontation with the mother, it was possible to establish

that she had been giving to her child (1) subcutaneous/intravenous regular insulin, (2) glyburide (glibenclamide in Europe), (3) progesterone, and (4) furosemide, occasionally on the same day. In addition, the mother later admitted of having administered laxative to induce the episodes of diarrhea that lead to previous hospitalizations.

After the separation of the mother from her son, we observed a rapid normalization of glucose and electrolytes profile, and the resolution of hirsutism.

## DISCUSSION

The case we reported had several features of the RMS, including alternance of fasting hypoglycemia



**FIGURE 2** Abdominal ultrasound showing nephrocalcinosis, a common feature of RMS cases.<sup>5</sup>

with postprandial hyperglycemia, hirsutism, and tubular dysfunction with nephrocalcinosis that mimicked Bartter syndrome.<sup>5</sup> These features may occur to a different extent in individuals with RMS during their lifetime.<sup>5,6</sup> RMS is caused by biallelic mutations of the INSR and is characterized, among other features, by extremely high insulin levels in an otherwise lean subject (ie, severe insulin resistance). Unnecessary, factitious insulin injections induce hypoglycemia and high immunoreactive insulin levels in the patient,<sup>7</sup> but can be spotted by simultaneous measurement of insulin and c-peptide demonstrating suppression of endogenous insulin secretion (ie, low/undetectable c-peptide). In contrast, the simultaneous administration by the mother to her son of insulin, along with a long-acting insulin secretagogue (glyburide), was a strong confounding factor, because this resulted in “normal” c-peptide levels, and made the interpretation of these laboratory tests repeatedly puzzling (Table 1). Two more confounding factors were hirsutism, a common finding of RMS,<sup>4–6</sup> which was caused by the administration of progesterone, and the Bartter-like phenotype described in patients with syndromes of severe insulin resistance such as RMS and Donohue syndrome.<sup>5,8,9</sup> The latter was maybe the outcome of long-term factitious furosemide dispensation that can result in hypercalciuria, hypokalemia, and metabolic alkalosis after prolonged treatment. Finally, the infective episodes observed in our case (a common cause of death in patients with RMS and Donohue syndrome is infection) have to be attributed to the intravenous injections by the mother deliberately performed without antiseptic care. This quite exceptional drug combination makes our case unique among the current reports of induced illness in pediatrics, and resulted in a bumpy diagnostic pathway.

Genetic screening of INSR gene usually detects mutations in most patients clinically diagnosed with RMS.<sup>4–6,10,11</sup> Consequently, the negative results obtained with this analysis, along with some missing features of RMS (lack of coarse facies and of IUGR) and persistently puzzling laboratory results raised suspicion of an FI.<sup>1,12</sup> This hypothesis was reinforced by the close observation of the mother-son relationship that highlighted the extreme difficulty of the mother in managing the daily care of her son, her loneliness as the only caregiver, and her defensive attitude in front of criticisms and discussion of the diagnostic hypothesis.<sup>1</sup> An additional clue for an FI was the detection of hypoglycemic crisis only in the presence of the mother.<sup>1,12</sup>

In retrospect, our case presented several classic features of fabricated diseases<sup>1</sup> that might have increased the suspicion: (1) multiple hospitalizations; (2) the caregiver was a nurse; (3) the child had a severe, previous medical condition (neurodevelopment delay, epilepsy) requiring a high maternal involvement in his care; and (4) the mother had to deal with her son's care on her own.

The recognition of FI in a child represents a diagnostic challenge, and the delay between the onset of the first symptoms and the diagnosis is reported to be ~21.8 months.<sup>13</sup> During this time lag, children suffer from useless, invasive examinations and receive unnecessary medications, both of which can lead to permanent injuries, life-threatening complications, and death,<sup>1,13</sup> with the latter occurring in 6% to 10% of cases of FI<sup>13</sup> (and higher percentages in the case of poisoning).<sup>14</sup> The incidence of FI in children <16 years of age is believed to range between 0.5 and 2.0 per 100,000.<sup>2,7,15</sup> However, epidemiologic data may vary depending on the expertise of the health providers and the adopted

criteria for inclusion, and may result in the underestimation of the true number of cases.<sup>1</sup> In an Italian report, the prevalence of a factitious disorder was ~1.8% of children referred to a pediatric unit (14/751)<sup>16</sup> with the so-called Munchausen-by-proxy syndrome identified in 0.53% of the examined cohort.

This case represents a paradigmatic model of how induced illness may simulate true medical conditions, and how physicians are usually induced to search for what they know. Because our group had a previous experience of 2 cases of RMS, we were led to recognize in the child's symptoms and signs what we had learned by our past experience, inhibiting our objective abilities.

## CONCLUSIONS

A detailed and deep clinical history, and the careful observation of patients and their caregivers are mandatory in each case of suspected FI in a child.

## ABBREVIATIONS

CGMS: continuous glucose monitoring system  
INSR: insulin receptor  
FI: fabricated illness  
RMS: Rabson-Mendenhall syndrome

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