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Case Report

Lessons learned from an unusual case of severe hypoglycemia

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ABSTRACT

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We are hereby reporting on a woman with type 1 diabetes getting insulin, 4 shots a day, and referring to us for an episode of severe hypoglycemia occurred after vigorously rubbing a lipo-hypertrophy (LH). She had always injected insulin into an abdominal LH area but had never suffered from any hypoglycemic event (Hypo) during the last period. Nevertheless her history included frequent Hypos, mostly mild-to-moderate but sometimes severe and eventually ending into unconsciousness and her glycemic control was poor (HbA1c 8.3%, mean FPG 161 ± 22 mg/dl, mean PPG 218 ± 51 mg/dl, glycemic variability (106 ± 44 mg/dl)). In fact, all of a sudden she rubbed vigorously the LH area trying to get rid of the abdominal skin thickening and soon after a severe Hypo occurred causing her to need for emergency medical assistance. When back at home, she corrected her technique and carefully refrained from inject insulin into the LH so that after six months the lesion disappeared, glycemic control improved and no Hypo occurred any more. Based on the recent publication reporting on a woman with a large LH consisting of thickened skin surrounding some fluid containing insulin at concentrations 300 fold those in blood, we hypothesize that such severe depended on massive insulin release from rubbed skin stores into the blood stream.

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1. Case history

A 35 year old lady who had suffered from Type 1 diabetes mellitus (T1DM) for ten years reported to our clinic. With a 154 cm height, and a 56 kg weight (BMI 23.3 kg/m^2), she was on a basal-bolus regimen consisting of 3 pre-meal lispro injections (18 I.U. as a whole) and a bedtime long-acting analogue administration (15 I.U. glargine). One year before her HbA1c was 7.1% (56 mmol/mol) and during the last month her mean glucose levels were 126 ± 15 mg/dl before meals and 189 ± 23 mg/dl 2 h after, being glycemic variability (GV defined according to Giorda et al., 2015 [1]) 68 ± 18 mg/dl. Her lipids, creatinine, urate, transaminases, bilirubin, blood cell and urine counts, blood pressure and heart rate ($120/80 \text{ mmHg}$ and 80 bpm, respectively), as well as, physical examination were normal. No eye, kidney or peripheral/autonomic nerve complications were present. No hypoglycemic event (Hypo) occurred during the last month either, as opposed to several previously recorded, even severe, Hypos, eventually ending into unconsciousness.

2. Anecdotal report

When asked how many and severe her Hypos had been during the last 2 years, she said her Hypo rate was about twice a week but she

almost never became unconscious and anyway got immediately better after ingesting some food or glucose despite having to face quite often and during the previous 6 months she experienced four severe Hypos, the last one causing unconsciousness (T-6). Her husband, who was there at the moment and assisted her, helped us get a narrative of the episode: it was summer and, due to her strong desire to wear a bikini, she tried to get rid of a swelling to the right of her navel which, being as big as a mandarin, was easily seen by anybody. She therefore used a soothing cream to rub it long and deeply enough to get weak in her lower limbs and soon develop tremors and unconsciousness. In a rescue effort, her husband immediately checked her capillary glucose and found very low levels, i.e. 35 mg/dl. Being unconscious, she could neither swallow nor get anything in her nose through a syringe, so he tried to perform an intramuscular glucagon injection but unfortunately the latter had got one month outdated in the refrigerator (it had been kept there for a long time waiting for any - never-occurring - severe Hypos). He then called the emergency number 118: within a few minutes the health care personnel arrived and took prompt steps by confirming the diagnosis and infusing 40 ml of a highly concentrated glucose solution (33%) followed immediately by 500 ml of a less concentrated one (10%) into her brachial vein. The patient took about 30 min to gradually regain consciousness and glucose levels progressively recovered until getting steadily normal so that there was no need for hospitalization. Accurate anamnestic investigations ruled out any insulin administration errors, food intake variations, incongruous exercise bouts or gastrointestinal symptoms including vomiting and diarrhea.

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Table 1

Comparison between mean values (\pm SD) of FPG, PPG, GV, HbA1c and the rate of HYPOs by severity during the 6 months before and after the accident.

	FPG mg/dl (M \pm SD)	PPG mg/dl (M \pm SD)	GV pre/post meal (mg/dl) (M \pm SD)	HbA1c (%)	Severe HYPOS in 6 months	Symptomatic HYPOs in 6 months
T -6	161 \pm 22	218 \pm 51	106 \pm 44	8.3	4	26
T +6	126 \pm 15	189 \pm 23	68 \pm 18	7.1	0	6
p	<0.05	<0.05	<0.05	<0.01		

M=mean value; SD=standard deviation; FPG=fasting plasma glucose; PP=post-prandial plasma glucose; GV=glucose variability.

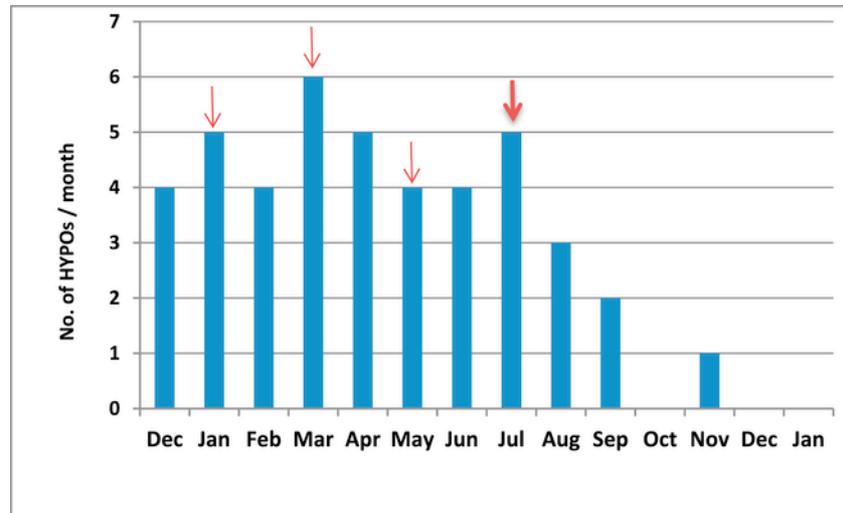


Fig. 1. Monthly Hypo rates before and after the accident occurred in July. Arrows point to severe hypos and the thick arrow points to the very severe one occurred in July and described in this case story.

She provided us with capillary glucose recordings from 6 months before the reported accident (T-6) and from the following ones until the present visit (T+6). Mean and SD values are reported in Table 1 and Hypo monthly rate in Fig. 1.

The clinical trend proved to be completely different as all metabolic parameters improved significantly, severe Hypos disappeared and mild to moderate Hypos progressively declined during the second semester. An interesting accompanying phenomenon was also observed: insulin requirement decreased by about 15% during the post-accident period.

3. Clinical considerations

1. Taken together, symptoms preceding and accompanying the unconsciousness episode, capillary glucose levels observed during the accident and the fast responsivity to intravenous glucose infusion point beyonding doubt to an episode of severe hypoglycemia;
2. The severe Hypo has to be defined as unexplained because no common factors eventually leading to hypoglycemia were identified [1,2].
3. The main cause of unexplained hypoglycemia is represented by insulin injection into LH nodules [2,3].
4. The patient admitted she had been vigorously rubbing a swelling close to her navel where she had repeatedly injected insulin for months.
5. In agreement with literature reports, repeated insulin injection into the same site and the disappearance of the swelling during the post-accident semester strongly suggest the swelling to be due to LH which in fact vanished with the change in injection strategies described by the patient [3,4].

4. Additional medical history

Further investigations on a possible causal relationship between rubbing the swelling and experiencing a severe Hypo immediately after got us to know that the patient:

1. Did not rotate injection sites correctly
2. Repeatedly used the same needle
3. Often injected ice-cold insulin and
4. Did not feel cold when doing so
5. Did not feel any ache or burning after injection
6. Reversed her above mentioned behaviour (which is known to cause LH) after the accident

5. Lessons learned from the clinical case

In our view it is doubtless that the presence of an abdominal swelling, which the patient preferred to inject into all the time, had a key role in the genesis of the above described accident. Based on the anamnestic finding of many factors known to cause LH [3], as well as, both the disappearance of severe Hypos and the dramatic decrease in the rate of non-severe Hypos after refraining for six months from injecting insulin into the interested area, such swelling could only reflect the presence of LH [4,5].

Now, the reason why the described Hypo had been so severe deserves a convincing explanation. The relationship between Hypos and LH areas has been known for a long time and in fact a quite high rate of mostly mild to moderate Hypos appeared in our patients' history but that was the very first time such a severe Hypo occurred in her ten year disease duration [2,3,5]. The effects of vigorous rubbing can-

not be underestimated either in consideration of a recent report in the literature: a very large area characterized by ultrasound as a partially cystic LH lesion was found to contain insulin at concentrations 300 fold those in blood [6]. This supports the hypothesis that rubbing represented a mechanical action eventually inducing massive insulin release into the blood stream. The time relationships between the two events is also in agreement with such hypothesis and with the national guidelines indications strongly discouraging post-injection skin rubbing in both healthy and LH areas [7].

5.1. Limitations

Our hypothesis, despite being based on sound indirect considerations, is only speculative because it lacks any indisputable objective support.

Conflicts of interest

The Authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.dsx.2019.01.033>.

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