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SIGNIFICANCE OF SPECIFIC IMMUNOSSAYS IN DETECTION OF INSULIN ANALOGS IN FACTIOUS HYPOGLYCEMIA IN INVESTIGATION: 3 CASE REPORTS.

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ABSTRACT

Objective: The aim is to highlight the importance of integrating specific insulin analog immune assays in the evaluation of hypoglycemic disorder investigations. **Methods:** We describe clinical, and laboratory findings of three study patients presented with spontaneous hypoglycemia and review the current relevant literature regarding methods of detecting suspicious factious use of insulin analogs by different insulin immunoassays to establish the cause of hypoglycemia. **Results:** The serum samples taken at the time of hypoglycemia in all three patients showed low insulin and low c-peptide. Mitigating and excluding other causes of hypoglycemia, factitious hypoglycemia due to insulin analogues was suspected. As usual commercial insulin assays don't detect insulin analogues, Special immunoassays were performed to detect insulin analogues and high insulin levels in these assays confirmed factitious insulin analogue use. **Conclusion:** Clinicians should be aware of insulin analogues as potential cause of factious hypoglycemia and suitable insulin assays should be included in the algorhythm of investigations of hypoglycemia to detect the commonly used insulin analogues for proper diagnosis and management.

KEY WORDS: Factitious hypoglycemia, insulin analogs, Immunoassay of insulin analogs.

INTRODUCTION

Most of the present literature on evaluation of hypoglycemic disorders mention various drugs, factious use of insulin secretogogues, insulins as a cause of spontaneous hypoglycemia. Insulin analogues which are widely used now-a days and potential cause of factious hypoglycemia are not detected in routine commercial insulin assays done. Detection of insulin analogues needs specific immunoassays if suspected as a cause of hypoglycemia. The case series report high lights the importance of integrating specific insulin analogue immunoassays in evaluation of factious hypoglycemia if warranted.

Case Reports

Case no: 1 29 year male soldier not known to have any previous illness presented to ER with the complaints of recurrent episodes of excessive sweating, palpitations, dizziness of 2 weeks duration. Patient denied taking any medications. Physical examination was unremarkable. At the time of presentation blood glucose was 37.8 mg/dl. Blood samples were taken for appropriate investigations and 10% dextrose infusion was initiated. Patients symptoms improved and blood sugars are normalized. Complete blood count, LFT, and renal function were normal. The other specific laboratory test results are recorded in table: no1.

Case No2:

20 year male patient presented to ER complaining of sweating, palpitation tremor and dizziness of 1 day duration. History of similar episodes 2 years before was told to have hypoglycemia but no diagnosis mentioned. Patient had no history of any other significant illness in the past. And denied taking any medications. Physical examination was unremarkable. Blood glucose recorded in ER on arrival was 50.8 mg/dl. Relevant blood samples were taken to investigate hypoglycemia and 10% Dextrose infusion was started and the blood sugars normalized and symptoms relieved. Complete blood count, renal function and LFT were normal. The other relevant laboratory test results are given in Table No 1.

Case No 3:

24 year old female patient seen in ER complaining of sweating, palpitations, dizziness, tremor of 2 days duration. Patient was experiencing similar symptoms for the past several weeks. There was no history of any significant illness or surgeries in the past. Patient demined taking any medications or injections. Sister is a known case of Type 1 Diabetic taking insulin. Physical

examination was unremarkable. The blood glucose recorded in ER was 39.6 mg/dl. Blood samples were taken for workup of hypoglycemia and 10% dextrose infusion was started. Patient had prompt improvement on her symptoms. The complete blood count, renal function and LFT were normal. The results of other laboratory tests done are given in Table No 1.

Table no: 1 showing relevant laboratory results.

Case No	Blood glucose(mg/dl)	Insulin level (17.8-173 pmol/l)#	C-peptide level (0.37-1.47nmol/l)	TFT	Cortisol level (AM)	Sulfonuria screening	Insulin level with insulin analogue immunoassay (17.8-173 pmol/l)
Case No:1	37.8	1.3	0.032	Normal	349	Negative	194.46
Case no: 2	50.8	1.39	0.184	Normal	178	Negative	270
Case no:3	39.6	34	0.18	Normal	405	Negative	4167

#Routine commercial insulin assay

All the three case study patients were young without any past significant systemic illnesses presented to ER with the typical history suggestive of hypoglycemia. Significant persistent hypoglycemia was recorded in ER with glucochek and in laboratory. All of them denied taking any medications causing hypoglycemia. Extensive work up did not retrieve any evident cause for these hypoglycemias. The low insulin levels assayed by conventional insulin assay (Rocheelecsys/E170) and low c-peptide, raised the possibility of factious insulin analog abuse. As the insulin analogs are not detected by usual commercial insulin assays, the samples were analyzed by specific immune assays for insulin analogs (Architect: Abbott laboratories) and high levels were recorded consistent with an exogenous administration of insulin analogues. On basis of this biological clue the patients are further questioned and finally all three admitted self injection of insulin analogues. All patients were sent psychologist assessment.

DISCUSSION
Factious hypoglycemia secondary to surreptitious use of human insulin and insulin secretogogues has been reported in literature abundant.[1] Investigations for detecting factious hypoglycemia due to human insulin are well established by existing assay for insulin, c-peptide and proinsulin. Insulin analogs are modified form of human insulin molecule in order to enhance therapeutic effectiveness. Several new insulin analogs that are synthesized by recombinant DNA technology are available for clinical use and are widely prescribed.[2] The extensive use of insulin analogs in recent years make them accessible for surreptitious use to cause factious hypoglycemia. It's is suspected in patients presenting with unexplained hypoglycemia with routine investigations, particularly those with access to insulin. It's critical to identify these cases because of severe complications of hypoglycemia like seizures, neurological deficits, coma and death. The diagnosis of insulin analogs causing factious hypoglycemia is difficult because commercially available insulin assays

detect these synthetic insulins with varying sensitivity and cross reactivity.[3, 4, 5, and 6] As the complexity of modification to the native insulin increases, the capability of assay to detect those decreases. Interestingly most commercial insulin assay kits inserts don't contain information concerning assay cross sensitivity of different insulins. The present literature on evaluation of factious hypoglycemia not include specific immunoassays detecting insulin analogs (Table No: 2). Analogues.[7, 8] These agents have altered pharmacokinetics compared to regular human insulin. Dayaldasani et al carefully assessed cross reactivity five insulin analogues in three immunoassays.[3] An excellent editorial also high lightened the complex phenomenon as a new source of error in immune assays of different insulins. Nalbantoglu Elams O et al[10] in their research article gave comprehensive comparison of commercial insulin immunoassays. Even though in recent years insulin analogs are extensively used and abused, cases of factious hypoglycemia due to insulin analogs are probably under reported, because the commercially used insulin immunoassays fail to detect insulin There has been only four cases reports factious hypoglycemia due to insulin analogues in literature.[8, 9, 10] In this case report series we presented three apparently healthy persons presented with spontaneous hypog lycemia. The routine work up for the cause of hypoglycemia did not reveal any specific cause. The strong suspicion of factitious hypoglycemia and careful history suggestive of access to insulin analogs prompted us to perform special immunoassays to detect the insulin analogs which revealed high concentrations of insulin analogues confirming the diagnosis of factitious hypoglycemia

CONCLUSION
Clinicians should be aware that most commercial insulin assays don't detect recombinant insulin analogs. Failure to appreciate this could lead to misdiagnosis with all its medico legal implications and potentially costly further investigations if specific insulin assays for detecting insulin analogues are not performed.

Table no:2 Comparison of commercial insulin assays.[6,8,9,11,12,13,14]

	Roche Elecsys/ E170	Architect: Abbott laboratorory	Immune 2000 Seimen Health care	Access Beckman coulter	Advia Centaur Seiman	Cisbio international (Schering)	IMx Abbott	Coat-A Count (Seiman)
Human insulin	+	+	+	+	+	+	+	+
Aspart	-	+	+	+	+	+	+	+
Lispro	-	+	+	+	+	+	+	+
Glulisine	-	+/-	-	N/A	_	_	N/A	N/A
Detemir	-	+	-	N/A	+	+	N/A	N/A
Glargine	_	+	+	+	+	+	+	+
N/A: not available								

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