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Re-interpreting the Appropriate Growth Hormone Response to Hypoglycaemia

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Abstract

Aims

'Critical samples' consist of assessment of an individual's metabolic and endocrine status during hypoglycaemia to evaluate for a pathological contributor towards aetiology of the episode. Growth hormone level is part of this work up to assess likelihood of GH deficiency. The aim of this study was to identify if the threshold used for growth hormone levels during hypoglycaemia in this clinic is appropriate and how likely values below this are to be indicative of growth hormone deficiency.

Methods

Retrospective review from a prospectively collected database of GH levels during hypoglycaemia as well as other growth parameters in paediatric population aged up to 16 years old over 12 months period at University Hospital Limerick.

Results

Forty blood samples were collected during the study period during hypoglycaemia. One sample was insufficient for analysis of GH level and of the remaining 39; only three (7.6 %) patients exhibited a "normal" GH response to hypoglycaemia of ≥ 7 µg/L.

Conclusion

No patient had documented GH deficiency or loss of height centiles, despite only 7.6% of patients (N=3/39) having "adequate" GH response during hypoglycaemia. These data suggest that the optimal level for GH during hypoglycaemia should be re-evaluated in larger prospective studies, to reduce unnecessary evaluation for GH deficiency with attendant anxiety and cost generated therein.

Introduction

Hypoglycaemia is a heterogeneous disorder with many different possible aetiologies. Clinically hypoglycaemia is defined as blood glucose level low enough to cause symptoms and signs of impaired brain function, generally accepted as ≤ 2.6 mmol/L. Hypoglycaemia is a potent stimulus for GH secretion[8]. Growth hormone is a key mediator of childhood growth, and its secretion is pulsatile in nature. Insulin tolerance test is one of many stimulation tests and has similar specificity to the others to determine the growth hormone status but risk of severe induced hypoglycaemia. [3, 5, 6] Other pharmacological stimuli include Arginine, Glucagon, Clonidine and L-Dopa. Optimum GH threshold in our clinic during hypoglycaemia episode is ≥ 7µg/L. Growth Hormone levels below this value are deemed suboptimal and indicates consideration of GH deficiency. In our recent clinical practice at UHL we have noted frequent suboptimal GH levels during hypoglycaemia episodes. The aim is to identify how likely values below this are to be indicative of GH deficiency in our hospital.

Methods

The study population consisted of paediatric patients aged up to 16 years old who had critical samples sent during hypoglycaemia over a 12 month period from 1st Jan 2018 until 30th Dec 2018 inclusive at University Hospital Limerick. Retrospective review from a prospectively collected database of GH, glucose levels and other growth parameters i.e., insulin-like growth factor (IGF)-1 levels, growth velocity/height centiles and growth hormone stimulation test (GHST). GH levels were subdivided into five subgroups: <1; 1-2.9; 3-4.9; 5-6.9; >7 µg/L.

Results

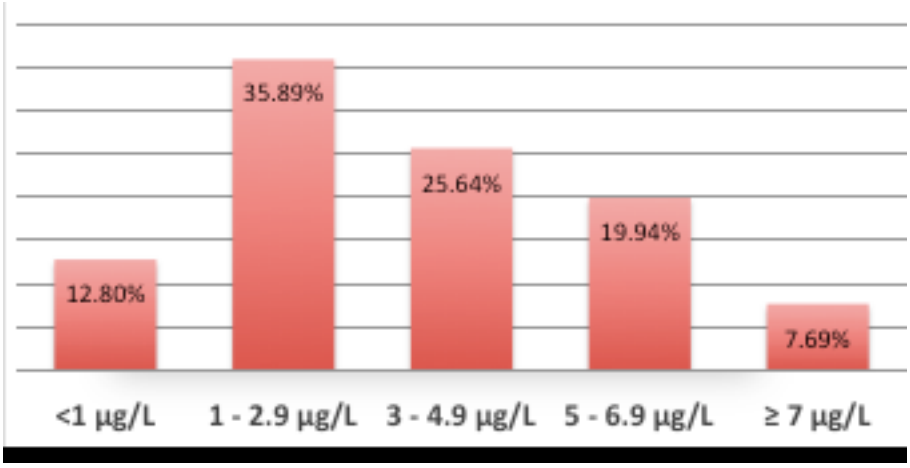
Forty blood samples were collected during the study period during hypoglycaemia. Growth hormone results according to 5 subgroups are shown in figure 1. One sample was insufficient for analysis of GH level and of the remaining 39, only three patients (7.6 %) exhibited a “normal” GH response to hypoglycaemia of ≥ 7 µg/L and thirty-six patients (92.3 %) had suboptimal GH levels. Data were skewed to the right with median GH reading of 3.19 µg/L and IQR value of 3.52 µg/L.

IGF-1 levels were available on 12/40 patients (30%). In one patient IGF-1 was low with GH level of 5.25 µg/L and a decelerating height centile but a subsequent normal GHST result with GH peak of 14.06 µg/L at 120 min.

Growth centiles/velocity were available on 19/40 patients (47.5%). Two patients had decelerating height centile, one as mentioned above and second one with background of global developmental delay, chromosome deletion and GH level of 3.56 µg/L was awaiting endocrine review during that time period.

Growth hormone stimulation testing was performed on 3/40 patients (7.5%) with GH levels of 3.3, 5.2, and 1.4 µg/L during hypoglycaemia and peak response of 10.2, 14.06 and 8.3 µg/L respectively at 120 minutes.

Fig 1: Percentage of growth hormone readings, within each range during hypoglycaemia work up.



Discussion

In our study the majority (92%) of GH readings collected during hypoglycaemia were deemed suboptimal by the traditional standard. Interestingly none of these patients were diagnosed with GH deficiency following further clinical assessment using auxology, IGF-1 levels, growth centiles and GHST, though the data in this group of the study were limited and incomplete.

The poor utility of GH measurement during hypoglcyaemia has been described previously. In 2008, Kelly et al highlighted that many children without GHD have extremely low GH levels[1] and that most did not have levels > 7 ng/ml (cortisol data were better but still not great). In 2016, Hawkes et al tried to overcome this my 'piggybacking' an assessment of glucagon-stimulated GH levels on top of an end-of-diagnostic-fast glucagon stimulation test and increased the number of children with confirmed sufficient GH levels from 10% to 55%.[2] Based on these data, and the data from this study, it is unlikely that a single threshold will be found and the recommendation would more appropriately be to use additional clinical features to determine if GH testing is warranted. Alone, the hypoglycaemia GH measurement is very poorly specific (although one could make the same argument for GH stimulation testing having very poor specificity too,[3, 4] yet many centres only do one stimulation test).

In conclusion, our results highlight a very high proportion of extremely low GH levels. This supports findings from previous studies about the poor specificity of low GH in investigation of hypoglycaemia. When venepuncture is challenging in investigation of low blood sugar, GH measurement is probably the least useful parameter and should be the last sample to be taken.

Declaration of Conflicts of Interest:
The authors declare no conflict of interest.

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