Laboratory findings of 302 patients with hyperinsulinemic hypoglycemia at hypoglycemia.

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[BACKGROUND]
The diagnosis of hyperinsulinemic hypoglycemia (HH) is not always straightforward especially when the insulin levels are not very high. Other parameters such as inappropriately low levels of β-hydroxybutylate and free fatty acids at hypoglycemia are helpful, but a wide variation makes it difficult to draw definite cutoffs. In these patients, the diagnosis of hyperinsulinemic hypoglycemia is made most reliably by the controlled fasting tests which includes the glycemic response to glucagon tests. However, fasting tests are not easily performed for children. Often we still need to rely on the conventional biochemical parameters of the critical samples.

[AIM]
(1) To analyze the biochemical profiles of pediatric patients with HH after introduction of sensitive insulin assays.
(2) To find biochemical markers to differentiate transient versus persistent congenital HH.

[SUBJECTS]
302 Japanese patients (182 males and 120 females) who presented with HH (glucose < 3 mmol/L (54 mg/dL)) at age 0 – 96 months who were identified either by the 2011 National Survey of Congenital Hyperinsulinism in Japan or by the chart review of patients who were directly referred to Osaka City General Hospital. Of these, 167 (107 males and 60 females) were eventually diagnosed with transient hyperinsulinism and 135 (75 males and 60 females) with persistent hyperinsulinism. As controls, 28 (11 males and 17 females) patients with non-HH hypoglycemia were used. Hypoglycemia resolved in the transient HH group at the median age of 26 days (1-100 days)

[METHODS]
Questionnaires to the treating physicians and chart review. Insulin was measured by the CLIA, CLEIA, or ECLIA assays with the detection limit of 0.3-0.5 μU/mL. Undetectable insulin was expressed as 0.1 μU/mL for statistical analysis.

[RESULTS]

(Demographic features)

	Transient HH	Persistent HH	controls	p
Gender (M/F)	107/60	75/60	11/17	NS
Birth weight (g)				
median	2016	3056	2946	< 0.0001
range	660-4318	530-5658	527-3320	
Age at onset (d)				
median	0	1.5	288	< 0.0001
range	0-6930	0-1152	1-2016	
Total	167	135	28	

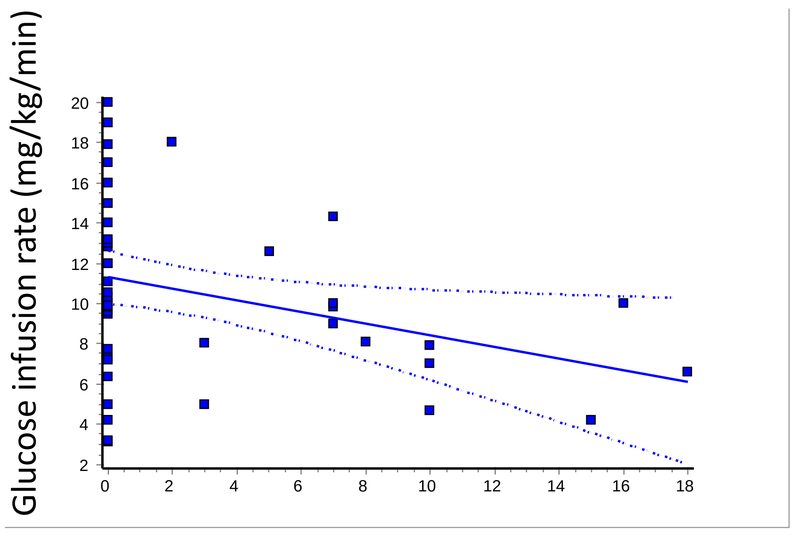
(GLUCOSE AND INSULIN AT PRESENTATION)

	Transient HH	Persistent HH	controls	p
Glucose (g/dl)				
median	27	32	45.5	< 0.0001
range	0-54	0-53	8-54	
Insulin (μU/mL)				
median	10	9.95	0.1	< 0.0001
range	1.26-200.9	0.6-205.6	0.1-1.2	

(β-HYDROXYBUTYLATE AND FREE FATTY ACIDS)

	Transient HH	Persistent HH	controls	p
β-hydroxybutylate (μmol/L)				
median	16	20.1	2669	< 0.0001
range	0-300	0.1-2784	1400-5680	
Free fatty acids (μmol/L)				
median	290	238	2570	< 0.0001
range	3.7-1573	6-1762	1230-3956	

(GLUCOSE INFUSION RATE TO MAINTAIN EUGLYCEMIA)



(LACTATE)

	Transient HH	Persistent HH	controls	p
Lactate (mg/dL)				
Median	25	15.6	13.7	0.0007
range	1.9-123.3	0-92.4	10-36.1	

(RECEIVER OPERATING CURVE ANALYSIS, persistent HH vs Control)

	Cutoff	Sensitivity (%)	Specificity (%)
Insulin (mU/mL)	1.05	98.5	91.7
β-hydroxybutylate (μmol/L)	2067	93.8	77.3
Free fatty acids (μmol/L)	1906	100	77.8

[DISCUSSION]
(1) By the routine use of insulin-specific assays with the detection limit of 0.3-0.5 μU/mL, the diagnostic accuracy of pediatric HH with relatively low insulin levels has been improved considerably compared with the previous experiences with the insulin detection limit of 2 μU/mL. Combined with the β-hydroxybutylate and free fatty acids, whose diagnostic specificities are relatively poor, it appears that the accuracy of conventional biochemical profile of critical samples has improved considereable to ameliorate the need for controlled fasting tests.
(2) Glucose infusion rate to maintain euglycemia tended to decline with age suggesting that a single cutoffs of 7-8 mg/kg/min can only be applied to newborns.
(3) Transient and persistent HH cannot be differentiated by insulin, β-hydroxybutylate, or free fatty acids. In addition to the clinical information of lower birth weight, elevated lactate at presentation might help differentiate transient HH from persistent HH. Lactate > 30 mg/dL has a sensitivity of 86.9% to detect transient HH although the specificity is low at 38.1%.

[CONCLUSION]
Current insulin assays to detect lower insulin levels have improved the diagnostic accuracy of critical sample analysis to diagnose pediatric HH.

[DISCLOSURE]
The authors have nothing to disclose.

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