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Undiagnosed Hypoglycemia Disorders in Children Detected When Hypoglycemia Occurs in the Setting of Illness: A Retrospective Study

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Undiagnosed Hypoglycemia Disorders in Children Detected When Hypoglycemia Occurs in the Setting of Illness: A Retrospective Study

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20 **Abstract**

21 **Objective:** Whether hypoglycemia incidentally detected during intercurrent illness in children
22 requires an endocrine workup remains controversial. This study aimed to determine the yield of
23 conducting a diagnostic evaluation in this setting, and to compare clinical and biochemical features
24 between patients ultimately diagnosed with a hypoglycemic disorder and those who were not.

25 **Design:** Single-center, retrospective review of children referred between January 2013 and December
26 2018 for evaluation of hypoglycemia (defined as plasma glucose <3.9 mmol/L [<70 mg/dL]) in the
27 setting of acute illness.

28 **Results:** 145 patients met eligibility criteria. A hypoglycemia disorder was identified in 12 patients
29 (8% of the cohort, 17% of those who underwent diagnostic fast). There were no cases in which
30 diagnosis was established in the absence of a diagnostic fast. Characteristics associated with
31 identifying an underlying disorder included younger age (1.03 years [IQR: 0.05, 1.54] v. 2.18 years
32 [IQR: 1.29, 3.99], p<0.001), higher bicarbonate level (22 ± 5.5 mmol/L v. 16 ± 3.6 mmol/L,
33 p<0.001), lower frequency of elevated plasma or urine ketones (25% v. 92%, p=0.004), and lower
34 frequency of other documented medical problems (17% v. 50%, p=0.03).

35 **Conclusions:** The yield of diagnostic evaluation among children with incidental detection of
36 hypoglycemia in the setting of illness is not insignificant. We thus recommend that all children with
37 hypoglycemia in the setting of illness undergo guided diagnostic evaluation. Younger age and
38 absence of ketosis and acidosis at presentation may serve as useful predictors for establishing a
39 diagnosis. Future studies are needed to confirm these findings.

40

41 **What is already known on this topic** – The prevalence of undiagnosed hypoglycemia disorders
42 among children seen in the emergency department for any clinical reason has been reported as 10-
43 28%. During illness, oral intake in children is often reduced. In this setting, incidentally
44 hypoglycemia is often attributed to prolonged fasting. Determining whether children with
45 hypoglycemia detected during illness require a dedicated endocrine evaluation has been limited by a
46 paucity of data.

47 **What this study adds** – In this cohort, 8% of children who presented with hypoglycemia in setting
48 of illness were found to have an underlying hypoglycemia disorder. Underlying hypoglycemia
49 diagnoses were only established in those children who underwent a comprehensive evaluation
50 including diagnostic fast. Younger age, higher bicarbonate level, and lower ketones at presentation
51 were associated with establishing a hypoglycemia diagnosis.

52 **How this study might affect research, practice or policy** – All children with hypoglycemia
53 detected in the setting of acute illness should undergo guided diagnostic evaluation.

1   Introduction

Incidental detection of hypoglycemia during childhood illness commonly occurs following prolonged starvation, in which glucose utilization exceeds glucose supply. Rarely, it may be the initial presentation of an underlying hypoglycemia disorder wherein missing the diagnosis carries a high risk of harm. The reported prevalence of undiagnosed hypoglycemia disorders among children seen in the emergency department for any reason ranges between 10 and 28% (1-3). However, these studies were not limited to children presenting with acute illness. Consequently, whether children with hypoglycemia detected during acute illness require an endocrine workup remains controversial. We sought to evaluate the yield of conducting an evaluation when hypoglycemia occurs in this setting and to describe the clinical and biochemical features of those children ultimately found to have underlying pathology.

2   Materials and Methods

A retrospective review was conducted of children referred to endocrinology for evaluation of hypoglycemia (plasma glucose <3.9 mmol/L [<70 mg/dL]) in the setting of acute illness at Children's Hospital of Philadelphia (CHOP) between January 2013 and December 2018. Billing records were utilized to obtain a list of inpatient and outpatient endocrine consults for hypoglycemia using ICD codes for "hypoglycemia, unspecified" (ICD-9 251.2 prior to October 2015, ICD-10 16.2 after October 2015). Additionally, inpatient billing records were manually searched for "hypoglycemia" as the consultation reason. Patients were included if they were <18 years of age and had both documented plasma glucose <3.9 mmol/L (<70 mg/dL) and illness symptoms (e.g., fever, vomiting, diarrhea, respiratory symptoms) at the time of presentation. Exclusion criteria included children with previously diagnosed hypoglycemia disorders, diabetes mellitus, or use of medications that can alter glucose metabolism (hypoglycemic agents, systemic steroids, chemotherapy, or beta-

77   blockers) within one month of presentation. A plasma glucose threshold of <3.9 mmol/L (<70

78   mg/dL) was utilized to define hypoglycemia in this study in keeping with established hypoglycemia

79   definitions (4, 5), and because below this threshold, neuroendocrine responses to hypoglycemia are

80   activated (6). Additionally, most infants and children are able to maintain plasma glucose above this

81   threshold after 15-18 hours of fasting (7).

82

83   Demographic, clinical, and biochemical data were extracted from the electronic health record (EHR).

84   Acute illness was categorized as: gastroenteritis, isolated vomiting, isolated diarrhea, upper

85   respiratory infection, otitis media, fever, and other. Illness categories were not exclusive; patients

86   were included in all categories for which there were documented symptoms. Height was categorized

87   as: short stature (<3 percentile for age), normal stature (≥3 and <97 percentile for age), and tall

88   stature (≥97 percentile for age). Height and weight were used to calculate weight-for-length

89   percentiles for patients <2 years of age and body mass index (BMI) percentiles for patients ≥2 years

90   of age. Weight was categorized as: underweight (weight-for-length/BMI <5 percentile for age),

91   normal weight (weight-for-length/BMI ≥5 and <85 percentile for age), overweight (weight-for-

92   length/BMI ≥85 and <95 percentile for age), and obese (weight-for-length/BMI ≥95 percentile for

93   age). Physical examination findings of interest included dysmorphic features, hepatomegaly, and

94   signs of suggestive of hypopituitarism (midline defects, microphallus in males).

95

96   Types of hypoglycemia evaluation performed included laboratory studies drawn at the time of

97   presentation, non-fasting laboratory studies obtained following presentation ("baseline evaluation"),

98   genetic testing, and diagnostic fasting studies, which were conducted as previously described

99   (standard protocol (8)). Evaluations were conducted at the discretion of the provider. This was

100 typically an emergency medicine provider at presentation. The decision to pursue diagnostic fasting

101 studies was made solely by endocrinologists. Standard practice at our center is to obtain baseline

102 metabolic studies (acylcarnitine profile, total and free carnitine levels, and urine organic acids) prior

103 to performing fasting studies when there is concern for a possible fatty acid oxidation disorder. To

104 facilitate comparison between groups, urine and blood ketone levels were combined into categories

105 wherein positive ketones were defined as either small or greater urine ketones or blood ketones ≥1

106 mmol/L.

107

108 The EHR was reviewed for additional episodes of hypoglycemia and for endocrine or metabolic

109 diagnoses (hormone deficiencies, disorders of insulin secretion/signaling, glycogen storage disease,

110 disorders of gluconeogenesis, and fatty acid oxidation disorders) made subsequent to the index event.

111 Duration of follow-up was calculated from index event and last contact dates.

112

113 This study was determined to be exempt by the CHOP Institutional Review Board. Patients were not

114 involved in the design or conduct of this study.

2.1 Statistical Analysis

116 Categorical variables were reported as proportions. Normally distributed continuous variables were

117 summarized using mean and standard deviation. Median and interquartile range were reported for

118 non-normally distributed continuous data. In comparing the clinical and biochemical characteristics

119 of patients ultimately diagnosed with a hypoglycemic disorder with those who were not, and patients

120 who underwent diagnostic fasting evaluation with those who did not, proportions were compared

121 using Fisher's exact test, t-tests were used to compare means of normally distributed data, and

122 Wilcoxon rank sum tests were used to compare medians of nonparametric data. All tests were two-

123 sided with $p<0.05$ set as the threshold for statistical significance.

3 Results

125 A total of 1410 patients were evaluated by endocrinology for hypoglycemia at CHOP between

126 January 2013 and December 2018. Of these, 145 patients met inclusion criteria, and their records

127 were reviewed (Figure 1). Characteristics of the cohort at time of presentation are summarized in

128 Table 1. Median age at presentation was 2 years and ranged from 2 days to 11 years. Abnormal

129 findings on physical examination were uncommon. Four patients had dysmorphism, three had

130 hepatomegaly, and one had macrocephaly. No patients had documented cleft lip or palate or

131 microphallus.

132

133 Thirteen percent of patients presented with altered mental status and 10% presented with seizure like

134 activity. Of the patients with a prior history of hypoglycemia, none had previously undergone a

135 diagnostic evaluation. Thirty-four percent of patients had recurrent episodes of hypoglycemia

136 following the index event. The median follow-up duration was 27 months (range: 0 days – 7.8 years).

3.1 Evaluations conducted

138 Laboratory evaluations performed at any point during follow-up varied considerably. At the time of

139 initial presentation with hypoglycemia, urine or plasma ketones were obtained in 57% of patients,

140 bicarbonate was obtained in 63%, transaminases were measured in 28%, and cortisol was obtained in

141 11%. Lactate, ammonia, insulin, c-peptide, free fatty acids, growth hormone, and metabolic studies

142 (acylcarnitine profile, total and free carnitine levels, and urine organic acids) were each obtained in

143 <10% of patients. Of the patients who had laboratory evaluation beyond glucose, ketones, and

144 bicarbonate at the time of initial presentation 50% had abnormal findings. Abnormal findings

145 included elevated transaminases (e.g., above the upper limit of normal) in 50% and elevated lactate in

146 18%. Cortisol was >276 nmol/L in all patients in whom it was obtained. Baseline evaluation was

147 obtained in 59% of patients with metabolic studies performed most frequently. Baseline evaluation

148 yielded abnormal findings in 29% of patients.

149

150 Of the 102 patients with plasma glucose <2.8 mmol/L (<50 mg/dL) on presentation, "critical sample"

151 labs including insulin, urine or plasma ketones, lactate, ammonia, cortisol, growth factors, and

152 acylcarnitine profile were obtained in 10%. Seventy percent of patients in whom a "critical sample"

153 was obtained had symptomatic hypoglycemia at the time of presentation.

154

155 A diagnostic fasting test was performed, either at the time of initial presentation or during a follow-

156 up admission, in 48% of patients. Twenty-five percent of the cohort had genetic testing performed

157 (Supplemental Table 1). Only two children had genetic testing without also undergoing a diagnostic

158 fast.

3.2 Identified hypoglycemia diagnoses

159

160 An underlying hypoglycemia disorder was identified in 12 patients (8%) all of whom underwent a

161 diagnostic fast. The clinical presentation, evaluation, and course of these patients is detailed in

162 Supplemental Table 2. The yield of performing a diagnostic fast in this study was 17%.

163

164 Hyperinsulinism was the most frequently identified etiology and was diagnosed in seven patients.

165 Additional diagnoses included inborn errors of metabolism in three patients, growth hormone

166 deficiency in one patient, and impaired hepatic insulin clearance due to acute hepatic insufficiency in

167 one patient. A final diagnosis was established in two patients in whom laboratory evaluation at

168 presentation other than glucose, ketones, and bicarbonate yielded abnormal findings. In both cases

169 (dihydrolipoamide dehydrogenase deficiency and impaired hepatic insulin clearance), transaminases

170 were elevated above the upper limit of normal for age.

171

172   An underlying genetic diagnosis was suggested based upon testing in four patients and included

173   hyperinsulinism due to an autosomal dominant mutation in *ABCC8*, hyperinsulinism associated with

174   Turner syndrome, isolated 3-methylcrotonyl-CoA carboxylase (MCC) deficiency, and

175   dihydrolipoamide dehydrogenase (DLD) deficiency.

3.3   Factors associated with identifying a specific hypoglycemia diagnosis

177   We compared clinical and biochemical characteristics at the time of presentation between the patients

178   ultimately diagnosed with an underlying etiology of hypoglycemia and those who were not (Table 2).

179   Younger age (1.03 years [IQR: 0.05, 1.54] v. 2.18 years [IQR: 1.29, 3.99], p<0.001) and higher

180   bicarbonate level (22 ± 5.5 mmol/L v. 16 ± 3.6 mmol/L, p<0.001) were associated with identifying

181   an underlying disorder. Patients diagnosed with a hypoglycemia disorder were less likely to have

182   elevated plasma or urine ketones at presentation (25% v. 92%, p=0.004) and were less likely to have

183   a documented history of other medical problems (17% v. 50%, p=0.03). No statistically significant

184   differences were observed between groups with regard to the other clinical or biochemical features

185   assessed.

186   Since a diagnostic fast was performed in all patients who ultimately had a final diagnosis established,

187   we evaluated whether there were any characteristics at presentation associated with conducting this

188   evaluation (Table 3). Median plasma glucose at presentation was lower in the group that underwent

189   diagnostic fast (2.2 mmol/L [40 mg/dL], IQR: 1.8, 2.7 mmol/L [32, 49 mg/dL] v. 2.6 mmol/L [47

190   mg/dL], IQR: 2.3, 3.0 mmol/L [41, 55 mg/dL], p=0.002). Additionally, the proportion of patients

191   with presenting plasma glucose <2.8 mmol/L (<50 mg/dL) was greater among those who underwent

192   a diagnostic fast compared to those who did not (80% v 62%, p=0.03).

4   Discussion

194 Eight percent of children who presented with hypoglycemia in setting of illness were found to have

195 an underlying hypoglycemia disorder. Underlying diagnoses were only established in children who

196 underwent a diagnostic fast, which was conducted in 48% of patients. The frequency of underlying

197 hypoglycemia disorders was thus two-fold higher (17%) among those who underwent diagnostic fast

198 as compared to the overall cohort.

199 These findings are in keeping with those of White, et al., who found that among children seen in the

200 emergency department for any reason with previously unrecognized hypoglycemia (plasma glucose

201 <2.8 mmol/L [50 mg/dL]), 10.6% were diagnosed with a hypoglycemia disorder (3). Diagnoses were

202 only identified in the children who underwent diagnostic evaluation (53%), such that 20% of those

203 who had a workup were found to have a hypoglycemia disorder. These findings emphasize that

204 without appropriate evaluation, children with underlying hypoglycemia disorders may not be

205 identified.

206 In a similar cohort of all comers to the emergency room in whom plasma glucose was <2.5 mmol/L

207 (<45 mg/dL), the frequency of previously unrecognized metabolic or endocrinologic disorders among

208 those without infectious diseases causing prolonged fasting was 11% (9). Pershad, et al. reported that

209 among children 1-5 years of age seen in the emergency department with an ICD code for

210 hypoglycemia and a plasma glucose <2.2 mmol/L (<40 mg/dL) or <3.3 mmol/L (<60 mg/dL) with

211 neuroglycopenic symptoms, 16% were diagnosed with an endocrine or metabolic disorder (1).

212 Details on the evaluations conducted and proportion of patients that underwent evaluation were

213 absent from these latter two studies. Notably, the frequency of finding an underlying hypoglycemia

214 disorder in our study is akin to that reported in the broader population of children seen in the

215 emergency department for any cause, potentially suggesting that the presence of illness symptoms

216 may be less pertinent than other clinical factors in identifying children with underlying hypoglycemia

217 disorders.

218 Weinstein, et al. found that 28% of children seen in the emergency department and incidentally

219 detected plasma glucose <2.8 mmol/L (<50 mg/dL) had an undiagnosed endocrine or metabolic

220 disorder (2). In this study, patients were prospectively recruited using software which permitted both

221 unbiased subject enrollment and "critical sample" collection prior to correction of hypoglycemia.

222 This is in contrast to the present study in which the decision to obtain a "critical sample" was at the

223 discretion of the provider and was obtained in only 10% of those with plasma glucose <2.8 mmol/L

224 (<50 mg/dL). The higher diagnosis rate in the Weinstein study, in which the decision to pursue

225 evaluation was automated and not based upon provider discretion, accentuates the previously absent

226 data to guide clinical practice in deciding which patients require further evaluation.

227 We found that young age and absence of acidosis and ketosis at presentation were associated with

228 identifying an underlying hypoglycemia disorder. When hypoglycemia occurs in a child as a

229 consequence of starvation (i.e., during illness), the child should have concomitantly elevated plasma

230 and urine ketone concentrations and decreased serum bicarbonate concentration (5). When this does

231 not occur, it should raise suspicion of dysregulated insulin secretion or disorders of fatty acid

232 oxidation. Our findings may have been influenced by the inclusion of neonates in the study

233 population, and in turn, the high proportion of children with previously undiagnosed hyperinsulinism.

234 Neither the duration of illness nor decreased oral intake was associated with establishing a

235 hypoglycemia diagnosis. However, the high level of missingness for these variables potentially limits

236 interpretation of these findings. Absence of documented medical or surgical comorbidities at

237 presentation also emerged as associated with establishing a diagnosis. Reasons for this finding are

238 less obvious but may also stem from the inclusion of neonates.

239 While the patients with growth hormone deficiency and acute hepatic insufficiency had clinical

240 features suggestive of the underlying etiology of hypoglycemia at presentation, the remainder did

241 not. In fact, the child with hyperinsulinism in the setting of mosaic Turner syndrome, which is a

242 recognized association (10), did not have classic phenotypic features of Turner syndrome. In this

243 child's case, a molecular diagnosis was incidentally uncovered during the genetic evaluation for

244 hyperinsulinism.

245 A genetic diagnosis was suggested based upon testing in 25% of patients in whom a hypoglycemia

246 disorder was identified. Overall, genetic testing yielded information supporting an underlying

247 etiology of hypoglycemia in 11% of patients in whom it was obtained. In a prior study of children

248 with ketotic hypoglycemia and nondiagnostic metabolic and endocrine evaluation, genetic testing

249 revealed mutations in genes involved in glycogen synthesis and degradation in 12% (11).

250 Interestingly, no cases of glycogen storage disease were identified in our cohort though it is notable

251 genetic evaluation was not universally performed.

252 Our findings need to be interpreted in light of several limitations. As a retrospective study, data was

253 subject to potential inconsistencies or omissions in documentation in the EHR. Although diagnoses

254 of hypoglycemia were biochemically confirmed, it is likely that potential subjects were not identified

255 because hypoglycemia was not listed as a diagnosis or reason for consultation. Decisions to obtain an

256 initial plasma glucose level, consult endocrinology, and pursue diagnostic evaluation were each at the

257 discretion of the provider. Selection bias could have resulted from differential decision-making at

258 each of these levels. We explored potential sources of bias stemming from the latter of these by

259 comparing those who did versus did not undergo a diagnostic fast, however this analysis fails to

260 capture the role of unmeasured factors driving differential selection of subjects. This was a single-

261 center study in which children were evaluated by endocrinologists with expertise in hypoglycemia

262 disorders at a large children's hospital. Findings may not be generalizable to different populations,

263 particularly those including children with different age distributions.

264 Despite these limitations, this study adds to the sparse body of literature examining the frequency of

265 underlying pathology among children with hypoglycemia during intercurrent illness. Our findings

266 highlight the importance of obtaining a "critical sample" or at a minimum, assays for bicarbonate and

267 beta-hydroxybutyrate at the time of hypoglycemia as these studies are both readily available and

268 informative in differentiating between categories of hypoglycemia disorders. This approach is in

269 keeping with Pediatric Endocrine Society recommendations for evaluation of hypoglycemia in

270 children (5). Without appropriate evaluation, these children may not be identified, and consequently,

271 appropriate treatment may not be implemented.

272 **5   Conclusions**

273 The high frequency of hypoglycemic disorders identified in this study underscores the critical

274 importance of investigating children with hypoglycemia during illness and argues against ascribing

275 findings to prolonged starvation. Endocrinology should be consulted to guide the diagnostic

276 evaluation. Young age and absence of ketosis and acidosis at presentation were identified as potential

277 predictors. These findings need to be confirmed in future studies.

278 **6   Funding and Competing Interests**

295 treating hyperinsulinism and postprandial hypoglycemia and has donated all financial proceeds from
296 these patents to the Children's Hospital of Philadelphia. Dr. De León participates on the advisory
297 boards of Soleno Therapeutics and the NIH: RADIANT Study and on the Scientific Advisory Board
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300 The other authors do not have any relevant disclosures to declare. The funding agencies did not have
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7   Author Contributions

303 O.A. and E.R. share first-authorship. O.A. and E.R. co-drafted the first version of the manuscript.
304 O.A. performed electronic health record data extraction. E.R. conducted data analyses. D.D.D.L.
305 conceptualized the work and edited the manuscript.

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338   **9   Supplementary Material**

339   **10   Data Availability Statement**

340   Data that support the findings of this study are included in this article and its supplementary material

341   file. Further enquiries can be directed to the corresponding author.

342 **Table 1. Cohort characteristics**

Patient Characteristics	N=145*
Age at presentation (years), median (IQR)	2.05 (1.21, 3.72)
Sex, % female (n)	55% (80)
Race/Ethnicity, % (n)	
White	62% (90)
Black	22% (32)
Asian	4% (6)
American Indian or Alaska Native	0.7% (1)
Other	9% (13)
Hispanic	2% (3)
Gestational age, % (n), N=138	
Preterm	16% (22)
Term	84% (116)
Birth weight (kg), mean ± SD, N=130	3.11 ± 0.72
History of perinatal stress, % (n), N=123	43% (53)
Past Medical History, % (n)	
Genetic Disorder	5.5% (8)
Neurodevelopment Disorder	16% (23)
Cardiac Disease	6.2% (9)
Pulmonary Disease	9.7% (14)
Gastroenterology Disease	20% (29)
Other	15% (22)
Weight category, % (n), N=140	
Underweight	13% (18)
Normal	71% (100)
Overweight	11% (16)
Obese	4.3% (6)
Height category, % (n), N=141	
Short stature	13% (18)
Normal stature	85% (120)
Tall stature	2.1% (3)
Prior history of hypoglycemia, % (n)	20% (29)
Presenting illness features, % (n)	
Gastroenteritis	25% (36)
Vomiting	44% (64)
Diarrhea	14% (20)
Upper respiratory tract infection	22% (32)
Otitis media	2.8% (4)
Fever	30% (44)
Other	12% (18)
Illness duration, % (n)	
1-3 days	59% (86)
≥ 4 days	26% (37)
Not recorded/unknown	15% (22)
History of decreased oral intake, % (n)	
1-3 days	46% (66)
≥ 4 days	8.3% (12)
Not recorded/unknown	46% (67)
Symptomatic hypoglycemia at presentation, % (n)	64% (93)

343 *unless otherwise noted

344

345 **Table 2. Characteristics of patients in whom an underlying etiology for hypoglycemia was**
346 **identified versus those without a diagnosis**

Variable N=145*	Diagnosis established N=12	No diagnosis established N=133	p-value
Age at presentation (years), median (IQR)	1.03 (0.05, 1.54)	2.18 (1.29, 3.99)	<0.001
Sex, % female (n)	67% (8)	54% (72)	0.55
Race, % White (n)	75% (9)	60% (81)	0.54
Ethnicity, % Hispanic (n)	0% (0)	2.3% (3)	>0.99
Weight category, % (n), N=140			0.27
Underweight	17% (2)	13% (16)	
Normal	83% (10)	70% (90)	
Overweight/Obese	0% (0)	17% (22)	
Height category, % (n), N=141			0.74
Short stature	17% (2)	12% (16)	
Normal stature	83% (10)	85% (110)	
Tall stature	0% (0)	2.3% (3)	
Prior history of hypoglycemia, % (n)	25% (3)	20% (26)	0.71
Past medical/surgical history, % (n)	17% (2)	50% (67)	0.03
Abnormal physical examination findings, % (n)	8.3% (1)	5.3% (7)	0.51
Presenting illness features, % (n)			
Gastroenteritis	25% (3)	25% (33)	>0.99
Vomiting	25% (3)	46% (61)	0.23
Diarrhea	25% (3)	13% (17)	0.22
Upper respiratory tract infection	17% (2)	23% (30)	>0.99
Otitis media	0% (0)	3.0% (4)	>0.99
Fever	33% (4)	30% (40)	0.76
Other	17% (2)	12% (16)	0.65
Illness duration, % (n), N=123			0.45
1-3 days	56% (5)	71% (81)	
≥ 4 days	44% (4)	29% (33)	
History of decreased oral intake, % (n), N=78			0.11
1-3 days	50% (2)	86.5% (64)	
≥ 4 days	50% (2)	13.5% (10)	
Symptomatic hypoglycemia at presentation, % (n)	50% (6)	65.4% (87)	0.35
Autonomic symptoms	0% (0)	6.0% (8)	>0.99
Neuroglycopenic symptoms	50% (6)	63% (84)	0.37
Labs at initial presentation			
Plasma glucose (mmol/L [mg/dL]), median (IQR)	2.5 (1.4, 2.7) [45 (26, 49)]	2.5 (2.1, 2.9) [45 (37, 52)]	0.42
Plasma glucose <2.8 mmol/L (<50 mg/dL), % (n)	83% (10)	69% (92)	0.51
Positive plasma or urine ketones, % (n), N=82	25% (1)	92% (72)	0.004
Serum bicarbonate (mmol/L), mean ± SD, N=91	22 ± 5.5	16 ± 3.6	<0.001
Other abnormal findings on presenting or baseline evaluation,† % (n), N=111	25% (2)	44% (45)	0.46

347 *unless otherwise noted, †including transaminases, lactate, ammonia, cortisol, growth hormone, IGF-I, IGFBP-3,
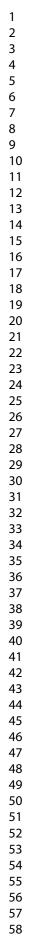348 acylcarnitine profile, carnitine profile, urine organic acids

349

350 **Table 3. Factors associated with performing diagnostic fast**
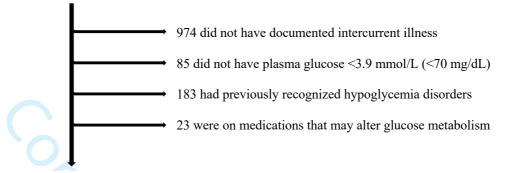
Variable N=145*	Diagnostic fast N=69	No diagnostic fast N=76	p-value
Age at presentation (years), median (IQR)	1.94 (1.23, 3.60)	2.12 (1.20, 3.96)	0.51
Sex, % female (n)	62% (43)	49% (37)	0.13
Race, % White (n)	68% (47)	57% (43)	0.17
Ethnicity, % Hispanic (n)	0% (0)	3.9% (3)	0.25
Weight category, % (n), N=140			0.68
Underweight	15% (10)	11% (8)	
Normal	74% (50)	72% (52)	
Overweight/Obese	12% (8)	17% (12)	
Height category, % (n), N=141			0.65
Short stature	15% (10)	11% (8)	
Normal stature	83% (57)	88% (63)	
Tall stature	2.9% (2)	1.4% (1)	
Prior history of hypoglycemia, % (n)	23% (16)	17% (13)	0.41
Past medical/surgical history, % (n)	42% (29)	53% (40)	0.25
Abnormal physical examination findings, % (n)	5.8% (4)	5.3% (4)	>0.99
Presenting illness features, % (n)			
Gastroenteritis	29% (20)	21% (16)	0.34
Vomiting	36% (25)	51% (39)	0.09
Diarrhea	17% (12)	11% (8)	0.34
Upper respiratory tract infection	25% (17)	20% (15)	0.55
Otitis media	1.5% (1)	4.0% (3)	0.62
Fever	30% (21)	30% (23)	>0.99
Other	15% (10)	11% (8)	0.62
Illness duration, % (n), N=123			>0.99
1-3 days	69% (38)	71% (48)	
≥ 4 days	31% (17)	29% (20)	
History of decreased oral intake, % (n), N=78			0.77
1-3 days	86% (31)	83% (35)	
≥ 4 days	14% (5)	17% (7)	
Symptomatic hypoglycemia at presentation, % (n)	71% (49)	58% (44)	0.12
Autonomic symptoms	4.4% (3)	6.6% (5)	0.72
Neuroglycopenic symptoms	70% (48)	55% (42)	0.09
Labs at initial presentation			
Plasma glucose (mmol/L [mg/dL]), median (IQR)	2.2 (1.8, 2.7) [40 (32, 49)]	2.6 (2.3, 3.0) [47 (41, 55)]	0.002
Plasma glucose <2.8 mmol/L (<50 mg/dL), % (n)	80% (55)	62% (47)	0.03
Positive plasma or urine ketones, % (n), N=82	83% (29)	94% (44)	0.16
Serum bicarbonate (mmol/L), mean ± SD, N=91	17 ± 4.0	16 ± 4.0	0.26
Other abnormal findings on presenting or baseline evaluation,† % (n), N=111	38% (22)	47% (25)	0.34

351 *unless otherwise noted, †including transaminases, lactate, ammonia, cortisol, growth hormone, IGF-I, IGFBP-3,
352 acylcarnitine profile, carnitine profile, urine organic acids

353   **Figures and Figure Legends**

354   **Figure 1. Consort diagram**

1410 patients were evaluated by endocrinology for
hypoglycemia between January 2013 and December 2018

974 did not have documented intercurrent illness

85 did not have plasma glucose <3.9 mmol/L (<70 mg/dL)

183 had previously recognized hypoglycemia disorders

23 were on medications that may alter glucose metabolism

145 patients included in analysis

Supplemental Table 1. Details of genetic testing performed

Of the genetic testing conducted, a commercial panel testing for glycogen storage diseases (sequencing of *AGL, G6PC, GAA, GBE1, GYS2, PFKM, PHKA1, PHKA2, PHKB, PHKG2, PYGL, PYGM, SLC2A2,* and *SLC37A4*) was obtained most frequently, in 14 patients. A ketotic hypoglycemia panel (sequencing and deletion/duplication analysis of *ACAT1, AGL, G6PC, GYS2, PHKA2, PHKB, PHKG2, PYGL, SLC16A1,* and *SLC37A4*) was obtained in 10 patients, hyperinsulinism panel (including sequencing of *ABCC8, KCNJ11, GCK, GLUD1* in all cases, with the addition of sequencing and deletion/duplication analysis of *ABCC8, KCNJ11, GLUD1, HADH, HNF1A, HNF4A, INSR, SLC16A1, UCP2* depending on the panel utilized) was obtained in six patients, fatty acid oxidation defect panel (sequencing and deletion/duplication analysis of *ACADVL*) was obtained in five patients, isolated *SLC16A1* mutation analysis was performed in three patients, and one patient had a commercial metabolic hypoglycemia panel (sequencing of *ACAT1, AGL, ALDOB, FBP1, G6PC, GALT, GYS2, HMGCL, MLYCD, OXCT1, PC, PCK1, PCK2, PGM1, PHKA2, PHKB, PHKG2, PYGL, SLC16A1, SLC2A2,* and *SLC37A4*) obtained. One child had targeted testing for Russel Silver syndrome based upon clinical examination findings. Chromosomal microarray was obtained in one patient and four patients had whole exome sequencing.

Supplemental Table 2. Summary of patients with identified hypoglycemia diagnoses

History and initial presentation	Evaluation findings	Treatment and Course
Growth hormone deficiency		
Term male, history of uninvestigated neonatal hypoglycemia. Presented at 10 months with vomiting, irritability, and POC PG of 32 mg/dL. Length z score -2.24, weight-for-length 80%ile.	Ketotic hypoglycemia (PG 52 mg/dL, BOHB 2.3 mmol/L) with normal lactate and cortisol (20 mcg/dL) but low GH 0.97 ng/mL. Peak GH after stimulation (arginine/clonidine) was 9.7 ng/mL and MRI revealed a small pituitary gland with possible ectopic pituitary tissue.	Initiated GH with resolution of hypoglycemia. Remains on GH replacement at 9 years of age.
Fatty acid oxidation disorder		
23-month-old female without significant past medical history presented with seizure and POC PG 20 mg/dL in setting of gastroenteritis.	Hypoketotic hypoglycemia with hyperfattyacidemia (PG 39 mg/dL, BOHB 1.4 mmol/L, FFA 3.98 mmol/L). Acylcarnitine profile revealed mild increase of C14:1 and C14:2 and UOA showed markedly increased dicarboxylic acids. Sequencing of *ACADVL* was negative, however, fatty acid oxidation probe of fibroblasts demonstrated significantly reduced oxidation of palmitate, consistent with impaired long-chain fatty acid oxidation.	Dextrose-containing fluids every 2 hours with illness. Multiple additional episodes of hypoglycemia during illness, one requiring hospitalization.
Dihydrolipoamide dehydrogenase (DLD) deficiency		
14-month-old male without significant medical history presented with gastroenteritis, lethargy, seizures, and PG 9 mg/dL.	Hypoglycemia with lactic acidosis and abnormal urine organic acid profile (PG 40 mg/dL, BOHB 1.3 mmol/L, FFA 2.5 mmol/L, lactate 5.2 mmol/L, ammonia 18 µmol/L, UOA: increased lactate, ketone, 2OH-glutaric acid, TCA cycle intermediates, 2-keto-glutaric acid, 2OH-adipic acid and glutaric acid). WES identified compound heterozygous variants in *DLD* Gly229Cys / Ser258Pro.	Low-protein diet. Numerous admissions for hypoglycemia and intermittent hepatic dysfunction.
3 methylcrotonyl-CoA carboxylase deficiency		
18-month-old female without significant past medical history presented with vomiting, lethargy, PG 49 mg/dL, and HCO3 16 mmol/L.	Ketotic hypoglycemia with abnormal urine organic acid profile (PG 52 mg/dL, BOHB 3.9 mmol/L, lactate 1.2 mmol/L, ammonia <9 µmol/L, acylcarnitine profile: moderate increase of C5OH-carnitine, UOA: increased 3-methylcrotonylglycine, lactic acid, 3-hydroxy-isovalerate, consistent with deficiency in 3 methylcrotonyl-CoA carboxylase. *MCCC1* sequencing identified a heterozygous novel pathogenic frameshift variant (Ser622Pro).	Limit fasting. Glucose meter and ketone meter monitoring. Multiple episodes of ketosis during illness, all managed at home.
Hyperinsulinism		
Term female born AGA, limited prenatal care. Presented at 5 days of age with jaundice and diarrhea due to rotavirus. POC PG 49 mg/dL, HCO3 23 mmol/L.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon on fast at 11 days of age (PG 57 mg/dL, BOHB 1.2 mmol/L, FFA 1.04 mmol/L, insulin <2 µIU/mL, C-peptide 0.22 ng/mL, IGFBP-1 167 ng/mL, ammonia 27 µmol/L, cortisol 25 mcg/dL, GH 10.2 ng/mL, Δ PG +45 mg/dl post-glucagon). Fasted 12 hours with PG >70 mg/dL. Genetic testing not performed. Presumed PSI-HI.	Diazoxide not initiated given fasting tolerance. Glucagon PRN, glucose meter monitoring. At 7 months of age, no PG <70 mg/dL on home monitoring.
Term female born AGA to GBS+ mother. Presented at 4 days of age with fever, irritability, POC PG 36 mg/dL, and HCO3 14 mg/dL. Infectious work-up was negative.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon on fast at 14 days of age (PG 43mg/dL, BOHB 0.8 mmol/L, FFA 0.8 mmol/L, insulin <2 µIU/mL, C-peptide 0.16 ng/mL, IGFBP-1 144 ng/mL, ammonia 39 µmol /L, cortisol 17 mcg/dL, GH 18 ng/mL, Δ PG +40 mg/dl post-glucagon). Fasted 8 hours with PG >70 mg/dL. Sequencing of *ABCC8*, *KCNJ11*, *GCK*, and *GLUD1* identified VUS in *GLUD1* (Ala49Thr).	Diazoxide not initiated given fasting tolerance. Limit fasting to 8 hours, glucagon PRN, glucose meter monitoring. Lost to follow-up.
Term male born SGA, history of uninvestigated neonatal hypoglycemia. Presented at 1 month of age with	Hypoketotic hypoglycemia with hypofattyacidemia (PG 50 mg/dL, BOHB 0.62 mmol/L, FFA 0.57 mmol/L, insulin <2 µIU/mL, C-peptide 0.21 ng/mL, lactate 0.8 mmol/L, ammonia 32 µmol/L, cortisol 10 mcg/dL, GH 4.08 ng/mL, glucagon stimulation not performed). Fasted 12	Glucagon PRN, glucose meter. Repeat fast at age 9 months demonstrated resolution of HI

fever, POC PG 58 mg/dL, and POC BOHB <0.3 mmol/L. + parechovirus.	hours with PG >70 mg/dL. Sequencing and del/dup of *ABCC8*, *KCNJ11* and sequencing of *GCK*, *GLUD1*, *HADH*, *HNF1A*, *HNF4A*, *SLC16A1,* and *UCP2* was negative.	(PG 42 mg/dL, BOHB 2.4 mmol/L, IGFBP-1 723 ng/mL).
Term male infant born with AGA. Presented at 2 days with diarrhea, irritability, and POC PG 49 mg/dL. Required max GIR 13 mg/kg/min. Found to have shigella enteritis.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon on fast at 8 days of age (PG 44 mg/dL, BOHB 0.9, FFA 0.72 mmol/L, insulin <2 μIU/mL, C-peptide 0.22 ng/mL, lactate 1.3 mmol/L, ammonia 19 μmol/L, cortisol 6 mcg/dl, GH 4.84 ng/mL, Δ PG +30 mg/dl post-glucagon). Fasted <3 hours with PG >70 mg/dL. Sequencing and del/dup of *ABCC8, KCNJ11, GLUD1, HADH, HNF1A, HNF4A, INSR, SLC16A1,* and *UCP2* and sequencing of *GCK* was negative.	Diazoxide 5 mg/kg/d, glucagon PRN, glucose meter monitoring. Transferred care to local endocrinologist at discharge.
Term female born AGA with failure to thrive and GERD. Presented at 5 months of age with fever, congestion, seizure, POC PG 42 mg/dL, HCO3 24 mmol/L, and negative urine ketones.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon (PG 42 mg/dL, BOHB <0.3 mmol/L, FFA 0.19 mmol/L, insulin <2 μIU/mL, C-peptide 0.35 ng/mL, lactate 1.3 mmol/L, ammonia 33 μmol/L, cortisol 11.6 mcg/dl, GH 8.07 ng/mL, Δ PG +45 mg/dl post-glucagon). Fasted <3 hours with PG >70 mg/dL. Sequencing and del/dup of *ABCC8, KCNJ11, GLUD1, HADH, HNF1A, HNF4A, INSR, SLC16A1,* and *UCP2* and sequencing *GCK* was negative for genes analyzed, revealed partial deletion of X chromosome, cytogenic analysis subsequently confirmed mosaicism for monosomy X and ring X confirming a diagnosis of Turner syndrome.	Enteral dextrose via G-tube. Later started lanreotide. At age 5 years, repeat fast off therapy demonstrated a safe fasting tolerance (PG >70 for 12 hours) but continued evidence of HI.
Female born at 34 weeks, SGA with heterotaxy syndrome. Presented at 18 months with fever, URI, diarrhea, POC PG 54 mg/dL, HCO3 28 mmol/L, and negative urine ketones.	Hypoketotic hypoglycemia with glycemic response to glucagon (PG 50 mg/dL, BOHB 1.7 mmol/L, FFA 2.1 mmol/L, insulin <2 μIU/mL, C-peptide 0.3 ng/mL, lactate 1.8 mmol/L, ammonia <9 μmol/L, cortisol 8.5 mcg/dL, GH 1.6 ng/mL, Δ PG >30 mg/dl post-glucagon). Fasted 3 hours with PG >70 mg/dL. Sequencing and del/dup of *ABCC8, KCNJ11, GLUD1, HADH, HNF1A, HNF4A, INSR, SLC16A1,* and *UCP2* and sequencing of *GCK* was negative.	Enteral dextrose via G-tube. Required treatment through age 3 years when demonstrated ability to fast 18 hours with PG >70 mg/dL off treatment.
Term female with history of uninvestigated neonatal hypoglycemia. Presented at 18 months with gastroenteritis and POC PG 16 mg/dL.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon (PG 45mg/dL, BOHB 0.62 mmol/L, FFA 0.5 mmol/L, insulin < 1 μIU/mL, C-peptide 0.5 ng/mL, lactate 1.2 mmol/L, ammonia 33 μmol/L, cortisol 5.1 mcg/dL, Δ PG + 68 mg/dl post-glucagon). Sequencing and del/dup of *ABCC8*, *KCNJ11* and sequencing of *GCK* and *GLUD1* identified an autosomal dominant paternally inherited mutation in *ABCC8* (pSer1387del)	Enteral dextrose via G-tube and lanreotide. Overnight enteral dextrose discontinued by 3 years of age. Remains on lanreotide.
Impaired hepatic insulin clearance		
22-month-old female with fever, URI, gastroenteritis, PG 48 mg/dl, HCO3 25 mmol/L, AST 6774 U/L, ALT 4847 U/L, and prolonged PT and PTT. Diagnosed with acute hepatic insufficiency due to rhinovirus and enterovirus. Hypoglycemia persisted despite improved liver function.	Hypoketotic hypoglycemia with elevated insulin and appropriately low C-peptide (PG 50 mg/dL, BOHB <0.3 mmol/L, FFA 2.0 mmol/L, insulin 8.6 μIU/mL, C-peptide 0.3 ng/mL, lactate 2.0 mmol/L, ammonia 32 μmol/L, cortisol 18.6 mcg/dL, GH 1.53 ng/mL, no glycemic response to glucagon, normal acylcarnitine profile and UOA). Fasting study repeated x 3 with consistent results.	Enteral dextrose via NG-tube overnight. Discontinued at 26 months of age following repeat fast demonstrating resolution of inappropriate insulin action (PG 47 mg/dL, BOHB 3.0 mmol/L, FFA 3.46 mmol/L, insulin <2 μIU/mL, and C-peptide < 0.1 ng/mL).

AGA appropriate for gestational age, ALT alanine aminotransferase, AST aspartate aminotransferase, BOHB ß-hydroxybutyrate, FFA free fatty acids, GBS Group B *Streptococcus*, GERD gastroesophageal reflux disease, GH growth hormone, GIR glucose infusion rate, G-tube gastrostomy tube, HCO3 bicarbonate, HI hyperinsulinism, IGFBP-1 insulin-like growth factor binding protein 1, MRI magnetic resonance imaging, NG nasogastric tube, PG plasma glucose, POC point-of-care, PRN *pro re nata*, PSI-HI perinatal stress induced hyperinsulinism, PT prothrombin time, PTT partial thromboplastin time, SGA small for gestational age, TCA tricarboxylic acid cycle, UOA urine organic acids, URI upper respiratory infection, WES whole exome sequencing

Response to Reviewer Comments

(1) Definition of hypoglycaemia - the authors suggest that <3.9mmol/L is hypoglycaemia, but this is not correct. Their data includes (I think) 102 patients with actual hypoglycaemia, and the analysis should be restricted to those with genuine hypoglycaemia.

Clinical hypoglycemia is defined as a plasma glucose concentration low enough to cause symptoms and/or signs of impaired brain function. However, in children, hypoglycemia may be difficult to recognize because the signs and symptoms are nonspecific. A specific plasma glucose concentration cannot easily be used to define hypoglycemia, because the thresholds for the physiologic responses to hypoglycemia occur across a range of plasma glucose concentrations and these thresholds can be altered by the presence of other metabolic fuels.

However, despite these limitations, established normative values for plasma glucose exist (3.9-5.5 mmol/L, [70-100 mg/dL]) (1, 2). These normative ranges are the same for children and adults; most infants and children are able to maintain plasma glucose above 3.9 mmol/L (70 mg/dL) after 15-18 hours of fasting (2). Many established committees and guidelines, including the American Diabetes Association, define hypoglycemia as a plasma glucose <3.9 mmol/L (<70 mg/dL) because this has been recognized as the threshold for neuroendocrine responses to falling glucose in healthy individuals. (3).

Accordingly, a plasma glucose threshold of 70 mg/dL was utilized to define hypoglycemia in this study. We aimed to cast a wide net by setting the threshold to identify our cohort at <70 mg/dL, understanding that the yield of identifying those children who had an underlying hypoglycemia disorder would be higher the lower the threshold. Rational for the plasma glucose threshold used to define hypoglycemia in this study was added to the methods section (lines 77-81).

(2) The authors need to give an estimate of how many patients have presented to their institution with acute illness and hypoglycaemia, not just those then referred for endocrine opinion. (This is giving a selection bias in the study design). This will give a better estimate of how many acutely unwell patients with hypoglycaemia have an underlying disorder.

While the authors agree that inclusion of the total number of patients seen at the institution with hypoglycemia during presentation for acute illness would provide helpful context, collection of these data was outside the scope/feasibility of the present study. The role of selection bias in this study was expanded in the discussion section (lines 254-259). Additionally, throughout the discussion, this study's findings are placed into context of existing literature, including studies in which estimates of all patients presenting to the institution with biochemical hypoglycemia are described, providing additional framework for interpretation to the reader.

(3) There is no set list of "hypoglycemic disorders", and although there is some discussion of endocrine and metabolic causes this must be delineated

Delineation of diagnoses was added to the methods section (lines 109-110).

(4) I am concerned that many patients seem to have diagnostic fasts performed on "clinician decision"

but without a clear rationale for why these are all needed. In particular, fasting a patient who may have a fatty acid oxidation defect is medically negligent and dangerous – yet the paper suggests that a diagnosis could only be reached in those who had a fasting test. It is mandatory to obtain results from an acylcarnitine profile before a fast is undertaken. The authors should clarify their institution's protocol on this.

The methods section was revised to include clarification of the institutional protocol for pursuing diagnostic fast in children in whom a disorder of fatty acid oxidation is suspected (lines 101-103)

(5) Several of the diagnoses listed in Supplemental Table 2 do not need fasting test to make the diagnosis – this can be reached on the baseline evaluations. This should be clarified.

The discussion (lines 238-243) was edited for clarification as suggested.

(6) There is very little mention of "idiopathic ketotic hypoglycaemia" which is probably the commonest cause of hypoglycaemia presenting in an acute illness. The final explanation for the hypoglycaemia for all of the patients should be given - either "physiological hypoglycaemia" explained in a starved child with acute illness, or Ketotic Hypoglycaemia, or alternative diagnosis.

The question of distinguishing those children with appropriate fasting tolerance for age but prolonged starvation due to illness versus those with inappropriately foreshortened fasting tolerance for age gets to the heart of the rationale for this study. The authors were interested to evaluate the role duration of reduced oral intake (i.e.: "duration of fasting"), however these analyses were limited by the retrospective nature of the study. Consequently, distinguishing between children with physiological hypoglycemia due to prolonged starvation during acute illness and those with idiopathic ketotic hypoglycemia provoked by acute illness was not feasible. Future prospective studies in which these data are more uniformly collected would likely prove useful in elucidating this further. Differentiating between these groups, however, is less clinically relevant than the identification of those children with endocrine and metabolic causes of hypoglycemia that have high risk of harm if left untreated and that require specialist follow up – which this study directly addresses.

(7) The statistical analysis identifies higher bicarbonate and lower ketones as "risk factors" for being more likely to have an underlying diagnosis. The confusion over which patients were included in the various analyses (were they all hypoglycaemic?) makes this hard to interpret correctly. It would be important to give an explanation for these findings. Hypoketotic hypoglycaemia is abnormal - suggestive of hyperinsulinism or fatty acid oxidation defect. Normal bicarbonate levels may mean the blood gas was normal, or just be consistent with absence of ketosis. Further discussion is warranted.

At presentation, all patients had hypoglycemia (lines 137-138) as defined in the methods section as plasma glucose <3.9 mmol/L (<70 mg/dL). All patients for whom ketones or serum bicarbonate values were available in the medical record at the time of presentation were included in these analyses (N for each provided in Table 2). Discussion of the implication of findings of hypoketotic hypoglycemia is provided in the discussion lines 229-231.

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Undiagnosed Hypoglycemia Disorders in Children Detected When Hypoglycemia Occurs in the Setting of Illness: A Retrospective Study

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Undiagnosed Hypoglycemia Disorders in Children Detected When Hypoglycemia Occurs in the Setting of Illness: A Retrospective Study

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Abstract

Objective: Whether hypoglycemia incidentally detected during intercurrent illness in children requires an endocrine workup remains controversial. This study aimed to determine the yield of conducting a diagnostic evaluation in this setting, and to compare clinical and biochemical features between patients ultimately diagnosed with a hypoglycemic disorder and those who were not.

Design: Single-center, retrospective review of children referred between January 2013 and December 2018 for evaluation of hypoglycemia (defined as plasma glucose <3.9 mmol/L [<70 mg/dL]) in the setting of acute illness.

Results: 145 patients met eligibility criteria. A hypoglycemia disorder was identified in 12 patients (8% of the cohort, 17% of those who underwent diagnostic fast). There were no cases in which diagnosis was established in the absence of a diagnostic fast. Characteristics associated with identifying an underlying disorder included younger age (1.03 years [IQR: 0.05, 1.54] v. 2.18 years [IQR: 1.29, 3.99], p<0.001), higher bicarbonate level (22 ± 5.5 mmol/L v. 16 ± 3.6 mmol/L, p<0.001), lower frequency of elevated plasma or urine ketones (25% v. 92%, p=0.004), and lower frequency of other documented medical problems (17% v. 50%, p=0.03).

Conclusions: The yield of diagnostic evaluation among children with incidental detection of hypoglycemia in the setting of illness is not insignificant. We thus recommend that all children with hypoglycemia in the setting of illness undergo guided diagnostic evaluation. Younger age and absence of ketosis and acidosis at presentation may serve as useful predictors for establishing a diagnosis. Future studies are needed to confirm these findings.

What is already known on this topic – The prevalence of undiagnosed hypoglycemia disorders among children seen in the emergency department for any clinical reason has been reported as 10-28%. During illness, oral intake in children is often reduced. In this setting, incidentally hypoglycemia is often attributed to prolonged fasting. Determining whether children with hypoglycemia detected during illness require a dedicated endocrine evaluation has been limited by a paucity of data.

What this study adds – In this cohort, 8% of children who presented with hypoglycemia in setting of illness were found to have an underlying hypoglycemia disorder. Underlying hypoglycemia diagnoses were only established in those children who underwent a comprehensive evaluation including diagnostic fast. Younger age, higher bicarbonate level, and lower ketones at presentation were associated with establishing a hypoglycemia diagnosis.

How this study might affect research, practice or policy – All children with hypoglycemia detected in the setting of acute illness should undergo guided diagnostic evaluation.

1   Introduction

Incidental detection of hypoglycemia during childhood illness commonly occurs following prolonged

starvation, in which glucose utilization exceeds glucose supply. Rarely, it may be the initial

presentation of an underlying hypoglycemia disorder wherein missing the diagnosis carries a high

risk of harm. The reported prevalence of undiagnosed hypoglycemia disorders among children seen

in the emergency department for any reason ranges between 10 and 28% (1-3). However, these

studies were not limited to children presenting with acute illness. Consequently, whether children

with hypoglycemia detected during acute illness require an endocrine workup remains controversial.

We sought to evaluate the yield of conducting an evaluation when hypoglycemia occurs in this

setting and to describe the clinical and biochemical features of those children ultimately found to

have underlying pathology.

2   Materials and Methods

A retrospective review was conducted of children referred to endocrinology for evaluation of

hypoglycemia (plasma glucose <3.9 mmol/L [<70 mg/dL]) in the setting of acute illness at

Children's Hospital of Philadelphia (CHOP) between January 2013 and December 2018. Billing

records were utilized to obtain a list of inpatient and outpatient endocrine consults for hypoglycemia

using ICD codes for "hypoglycemia, unspecified" (ICD-9 251.2 prior to October 2015, ICD-10 16.2

after October 2015). Additionally, inpatient billing records were manually searched for

"hypoglycemia" as the consultation reason. Patients were included if they were <18 years of age and

had both documented plasma glucose <3.9 mmol/L (<70 mg/dL) and illness symptoms (e.g., fever,

vomiting, diarrhea, respiratory symptoms) at the time of presentation. Exclusion criteria included

children with previously diagnosed hypoglycemia disorders, diabetes mellitus, or use of medications

that can alter glucose metabolism (hypoglycemic agents, systemic steroids, chemotherapy, or beta-

77 blockers) within one month of presentation. A plasma glucose threshold of <3.9 mmol/L (<70

78 mg/dL) was utilized to define hypoglycemia in this study in keeping with established hypoglycemia

79 definitions (4, 5), and because below this threshold, neuroendocrine responses to hypoglycemia are

80 activated (6). Additionally, most infants and children are able to maintain plasma glucose above this

81 threshold after 15-18 hours of fasting (7).

82

83 Demographic, clinical, and biochemical data were extracted from the electronic health record (EHR).

84 Acute illness was categorized as: gastroenteritis, isolated vomiting, isolated diarrhea, upper

85 respiratory infection, otitis media, fever, and other. Illness categories were not exclusive; patients

86 were included in all categories for which there were documented symptoms. Height and weight were

87 used to calculate weight-for-length percentiles for patients <2 years of age and body mass index

88 (BMI) percentiles for patients ≥2 years of age. Weight status was categorized as: underweight

89 (weight-for-length/BMI <5 percentile for age), normal weight (weight-for-length/BMI ≥5 and <85

90 percentile for age), overweight (weight-for-length/BMI ≥85 and <95 percentile for age), and obese

91 (weight-for-length/BMI ≥95 percentile for age). Physical examination findings of interest included

92 dysmorphic features, hepatomegaly, and signs of suggestive of hypopituitarism (midline defects,

93 microphallus in males).

94

95 Types of hypoglycemia evaluation performed included laboratory studies drawn at the time of

96 presentation, non-fasting laboratory studies obtained following presentation ("baseline evaluation"),

97 genetic testing, and diagnostic fasting studies, which were conducted as previously described

98 (standard protocol (8)). Evaluations were conducted at the discretion of the provider. This was

99 typically an emergency medicine provider at presentation. The decision to pursue diagnostic fasting

100 studies was made solely by endocrinologists. Standard practice at our center is to obtain baseline

101 metabolic studies (acylcarnitine profile, total and free carnitine levels, and urine organic acids) prior

102 to performing fasting studies when there is concern for a possible fatty acid oxidation disorder. To

103 facilitate comparison between groups, urine and blood ketone levels were combined into categories

104 wherein positive ketones were defined as either small or greater urine ketones or blood ketones ≥ 1

105 mmol/L; ketones were otherwise defined as negative.

106

107 The EHR was reviewed for additional episodes of hypoglycemia and for endocrine or metabolic

108 diagnoses (hormone deficiencies, disorders of insulin secretion/signaling, glycogen storage disease,

109 disorders of gluconeogenesis, and fatty acid oxidation disorders) made subsequent to the index event.

110 Duration of follow-up was calculated from index event and last contact dates.

111

112 This study was determined to be exempt by the CHOP Institutional Review Board. Patients were not

113 involved in the design or conduct of this study.

114 **2.1 Statistical Analysis**

115 Categorical variables were reported as proportions. Normally distributed continuous variables were

116 summarized using mean and standard deviation. Median and interquartile range were reported for

117 non-normally distributed continuous data. In comparing the clinical and biochemical characteristics

118 of patients ultimately diagnosed with a hypoglycemic disorder with those who were not, and patients

119 who underwent diagnostic fasting evaluation with those who did not, proportions were compared

120 using Fisher's exact test, t-tests were used to compare means of normally distributed data, and

121 Wilcoxon rank sum tests were used to compare medians of nonparametric data. All tests were two-

122 sided with $p < 0.05$ set as the threshold for statistical significance.

123 **3   Results**

124 A total of 1410 patients were evaluated by endocrinology for hypoglycemia at CHOP between

125 January 2013 and December 2018. Of these, 145 patients met inclusion criteria, and their records

126 were reviewed (Figure 1). Characteristics of the cohort at time of presentation are summarized in

127 Table 1. Median age at presentation was 2 years and ranged from 2 days to 11 years. Abnormal

128 findings on physical examination were uncommon. Four patients had dysmorphism, three had

129 hepatomegaly, and one had macrocephaly. No patients had documented cleft lip or palate or

130 microphallus.

131

132 Thirteen percent of patients presented with altered mental status and 10% presented with seizure like

133 activity. Of the patients with a prior history of hypoglycemia, none had previously undergone a

134 diagnostic evaluation. Thirty-four percent of patients had recurrent episodes of hypoglycemia

135 following the index event. The median follow-up duration was 27 months (range: 0 days – 7.8 years).

3.1 Evaluations conducted

137 Laboratory evaluations performed at any point during follow-up varied considerably. At the time of

138 initial presentation with hypoglycemia, urine or plasma ketones were obtained in 57% of patients,

139 bicarbonate was obtained in 63%, transaminases were measured in 28%, and cortisol was obtained in

140 11%. Lactate, ammonia, insulin, c-peptide, free fatty acids, growth hormone, and metabolic studies

141 (acylcarnitine profile, total and free carnitine levels, and urine organic acids) were each obtained in

142 <10% of patients. Of the patients who had laboratory evaluation beyond glucose, ketones, and

143 bicarbonate at the time of initial presentation 50% had abnormal findings. Abnormal findings

144 included elevated transaminases (e.g., above the upper limit of normal) in 50% and elevated lactate in

145 18%. Cortisol was >276 nmol/L in all patients in whom it was obtained. Baseline evaluation was

146 obtained in 59% of patients with metabolic studies performed most frequently. Baseline evaluation

147 yielded abnormal findings in 29% of patients.

148

149   Of the 102 patients with plasma glucose <2.8 mmol/L (<50 mg/dL) on presentation, "critical sample"

150   labs including insulin, urine or plasma ketones, lactate, ammonia, cortisol, growth factors, and

151   acylcarnitine profile were obtained in 10%. Seventy percent of patients in whom a "critical sample"

152   was obtained had symptomatic hypoglycemia at the time of presentation.

153

154   A diagnostic fasting test was performed, either at the time of initial presentation or during a follow-

155   up admission, in 48% of patients. Twenty-five percent of the cohort had genetic testing performed

156   (Supplemental Table 1). Only two children had genetic testing without also undergoing a diagnostic

157   fast.

3.2   Identified hypoglycemia diagnoses

159   An underlying hypoglycemia disorder was identified in 12 patients (8%) all of whom underwent a

160   diagnostic fast. The clinical presentation, evaluation, and course of these patients is detailed in

161   Supplemental Table 2. The yield of performing a diagnostic fast in this study was 17%.

162

163   Hyperinsulinism was the most frequently identified etiology and was diagnosed in seven patients.

164   Additional diagnoses included inborn errors of metabolism in three patients, growth hormone

165   deficiency in one patient, and impaired hepatic insulin clearance due to acute hepatic insufficiency in

166   one patient. A final diagnosis was established in two patients in whom laboratory evaluation at

167   presentation other than glucose, ketones, and bicarbonate yielded abnormal findings. In both cases

168   (dihydrolipoamide dehydrogenase deficiency and impaired hepatic insulin clearance), transaminases

169   were elevated above the upper limit of normal for age.

170

171 An underlying genetic diagnosis was suggested based upon testing in four patients and included

172 hyperinsulinism due to an autosomal dominant mutation in *ABCC8*, hyperinsulinism associated with

173 Turner syndrome, isolated 3-methylcrotonyl-CoA carboxylase (MCC) deficiency, and

174 dihydrolipoamide dehydrogenase (DLD) deficiency.

3.3 Factors associated with identifying a specific hypoglycemia diagnosis

176 We compared clinical and biochemical characteristics at the time of presentation between the patients

177 ultimately diagnosed with an underlying etiology of hypoglycemia and those who were not (Table 2).

178 Younger age (1.03 years [IQR: 0.05, 1.54] v. 2.18 years [IQR: 1.29, 3.99], p<0.001) and higher

179 bicarbonate level (22 ± 5.5 mmol/L v. 16 ± 3.6 mmol/L, p<0.001) were associated with identifying

180 an underlying disorder. Weight-for-age percentile was lower in patients diagnosed with a

181 hypoglycemia disorder (13.1 [IQR: 1.7, 23.8] v. 31.0 [14.0, 59.5], p=0.02) but weight status (i.e.,

182 weight adjusted for length/height) did not statistically significantly differ between those who were

183 diagnosed with a hypoglycemia disorder and those who were not. Patients diagnosed with a

184 hypoglycemia disorder were less likely to have elevated plasma or urine ketones at presentation (25%

185 v. 92%, p=0.004) and were less likely to have a documented history of other medical problems (17%

186 v. 50%, p=0.03). No statistically significant differences were observed between groups with regard to

187 the other clinical or biochemical features assessed.

188 Since a diagnostic fast was performed in all patients who ultimately had a final diagnosis established,

189 we evaluated whether there were any characteristics at presentation associated with conducting this

190 evaluation (Table 3). Median plasma glucose at presentation was lower in the group that underwent

191 diagnostic fast (2.2 mmol/L [40 mg/dL], IQR: 1.8, 2.7 mmol/L [32, 49 mg/dL] v. 2.6 mmol/L [47

192 mg/dL], IQR: 2.3, 3.0 mmol/L [41, 55 mg/dL], p=0.002). Additionally, the proportion of patients

193 with presenting plasma glucose <2.8 mmol/L (<50 mg/dL) was greater among those who underwent

194 a diagnostic fast compared to those who did not (80% v 62%, p=0.03).

4 Discussion

196 Eight percent of children who presented with hypoglycemia in setting of illness were found to have

197 an underlying hypoglycemia disorder. Underlying diagnoses were only established in children who

198 underwent a diagnostic fast, which was conducted in 48% of patients. The frequency of underlying

199 hypoglycemia disorders was thus two-fold higher (17%) among those who underwent diagnostic fast

200 as compared to the overall cohort.

201 These findings are in keeping with those of White, et al., who found that among children seen in the

202 emergency department for any reason with previously unrecognized hypoglycemia (plasma glucose

203 <2.8 mmol/L [50 mg/dL]), 10.6% were diagnosed with a hypoglycemia disorder (3). Diagnoses were

204 only identified in the children who underwent diagnostic evaluation (53%), such that 20% of those

205 who had a workup were found to have a hypoglycemia disorder. These findings emphasize that

206 without appropriate evaluation, children with underlying hypoglycemia disorders may not be

207 identified.

208 In a similar cohort of all comers to the emergency room in whom plasma glucose was <2.5 mmol/L

209 (<45 mg/dL), the frequency of previously unrecognized metabolic or endocrinologic disorders among

210 those without infectious diseases causing prolonged fasting was 11% (9). Pershad, et al. reported that

211 among children 1-5 years of age seen in the emergency department with an ICD code for

212 hypoglycemia and a plasma glucose <2.2 mmol/L (<40 mg/dL) or <3.3 mmol/L (<60 mg/dL) with

213 neuroglycopenic symptoms, 16% were diagnosed with an endocrine or metabolic disorder (1).

214 Details on the evaluations conducted and proportion of patients that underwent evaluation were

215 absent from these latter two studies. Notably, the frequency of finding an underlying hypoglycemia

216 disorder in our study is akin to that reported in the broader population of children seen in the

217 emergency department for any cause, potentially suggesting that the presence of illness symptoms

218 may be less pertinent than other clinical factors in identifying children with underlying hypoglycemia

219 disorders.

220 Weinstein, et al. found that 28% of children seen in the emergency department and incidentally

221 detected plasma glucose <2.8 mmol/L (<50 mg/dL) had an undiagnosed endocrine or metabolic

222 disorder (2). In this study, patients were prospectively recruited using software which permitted both

223 unbiased subject enrollment and "critical sample" collection prior to correction of hypoglycemia.

224 This is in contrast to the present study in which the decision to obtain a "critical sample" was at the

225 discretion of the provider, typically an emergency medicine provider, and was obtained in only 10%

226 of those with plasma glucose <2.8 mmol/L (<50 mg/dL). Reasons for the low rate of "critical

227 sample" collection are unclear. The majority of children for whom a "critical sample" was obtained

228 had symptomatic hypoglycemia, and it is possible that prompt treatment of hypoglycemia was

229 prioritized over obtaining laboratory assessment in children able to tolerate oral carbohydrate

230 whereas "critical sample" laboratories were more likely to be obtained in children in whom

231 administration of intravenous dextrose was considered. The higher diagnosis rate in the Weinstein

232 study, in which the decision to pursue evaluation was automated and not based upon provider

233 discretion, accentuates the previously absent data to guide clinical practice in deciding which patients

234 require further evaluation.

235 We found that young age and absence of acidosis and ketosis at presentation were associated with

236 identifying an underlying hypoglycemia disorder. When hypoglycemia occurs in a child as a

237 consequence of starvation (i.e., during illness), the child should have concomitantly elevated plasma

238 and urine ketone concentrations and decreased serum bicarbonate concentration (5). When this does

239 not occur, it should raise suspicion of dysregulated insulin secretion or disorders of fatty acid

240 oxidation. Our findings may have been influenced by the inclusion of neonates in the study

241 population, and in turn, the high proportion of children with previously undiagnosed hyperinsulinism.

242 Neither the duration of illness nor decreased oral intake was associated with establishing a

243 hypoglycemia diagnosis. However, the high level of missingness for these variables potentially limits

244 interpretation of these findings. Children in whom a diagnosis was established had lower weight-for-

245 age, but weight status (weight adjusted for length/height) did not statistically significantly differ

246 between groups. Absence of documented medical or surgical comorbidities at presentation also

247 emerged as associated with establishing a diagnosis. Reasons for this finding are less obvious but

248 may also stem from the inclusion of neonates.

249 While the patients with growth hormone deficiency and acute hepatic insufficiency had clinical

250 features suggestive of the underlying etiology of hypoglycemia at presentation, the remainder did

251 not. In fact, the child with hyperinsulinism in the setting of mosaic Turner syndrome, which is a

252 recognized association (10), did not have classic phenotypic features of Turner syndrome. In this

253 child's case, a molecular diagnosis was incidentally uncovered during the genetic evaluation for

254 hyperinsulinism.

255 A genetic diagnosis was suggested based upon testing in 25% of patients in whom a hypoglycemia

256 disorder was identified. Overall, genetic testing yielded information supporting an underlying

257 etiology of hypoglycemia in 11% of patients in whom it was obtained. In a prior study of children

258 with ketotic hypoglycemia and nondiagnostic metabolic and endocrine evaluation, genetic testing

259 revealed mutations in genes involved in glycogen synthesis and degradation in 12% (11).

260 Interestingly, no cases of glycogen storage disease were identified in our cohort though it is notable

261 genetic evaluation was not universally performed.

262 Our findings need to be interpreted in light of several limitations. As a retrospective study, data was

263 subject to potential inconsistencies or omissions in documentation in the EHR. Although diagnoses

264 of hypoglycemia were biochemically confirmed, it is likely that potential subjects were not identified

265 because hypoglycemia was not listed as a diagnosis or reason for consultation. Decisions to obtain an

266 initial plasma glucose level, consult endocrinology, and pursue diagnostic evaluation were each at the

267 discretion of the provider. Selection bias could have resulted from differential decision-making at

268 each of these levels. We explored potential sources of bias stemming from the latter of these by

269 comparing those who did versus did not undergo a diagnostic fast, however this analysis fails to

270 capture the role of unmeasured factors driving differential selection of subjects. This was a single-

271 center study in which children were evaluated by endocrinologists with expertise in hypoglycemia

272 disorders at a large children's hospital. Findings may not be generalizable to different populations,

273 particularly those including children with different age distributions.

274 Despite these limitations, this study adds to the sparse body of literature examining the frequency of

275 underlying pathology among children with hypoglycemia during intercurrent illness. Our findings

276 highlight the importance of obtaining a "critical sample" or at a minimum, assays for bicarbonate and

277 beta-hydroxybutyrate at the time of hypoglycemia as these studies are both readily available and

278 informative in differentiating between categories of hypoglycemia disorders. This approach is in

279 keeping with Pediatric Endocrine Society recommendations for evaluation of hypoglycemia in

280 children (5). Without appropriate evaluation, these children may not be identified, and consequently,

281 appropriate treatment may not be implemented.

282 **5   Conclusions**

283 The high frequency of hypoglycemic disorders identified in this study underscores the critical

284 importance of investigating children with hypoglycemia during illness and argues against ascribing

285 findings to prolonged starvation. Endocrinology should be consulted to guide the diagnostic

286 evaluation. Young age and absence of ketosis and acidosis at presentation were identified as potential

287 predictors. These findings need to be confirmed in future studies.

6   Funding and Competing Interests

7   Author Contributions

313 O.A. and E.R. share first-authorship. O.A. and E.R. co-drafted the first version of the manuscript.
314 O.A. performed electronic health record data extraction. E.R. conducted data analyses. D.D.D.L.
315 conceptualized the work and edited the manuscript.

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9   Supplementary Material

10   Data Availability Statement

Data that support the findings of this study are included in this article and its supplementary material file. Further enquiries can be directed to the corresponding author.

352 **Table 1. Cohort characteristics**

Patient Characteristics	N=145*
Age at presentation (years), median (IQR)	2.05 (1.21, 3.72)
Sex, % female (n)	55% (80)
Race/Ethnicity, % (n)	
White	62% (90)
Black	22% (32)
Asian	4% (6)
American Indian or Alaska Native	0.7% (1)
Other	9% (13)
Hispanic	2% (3)
Gestational age, % (n), N=138	
Preterm	16% (22)
Term	84% (116)
Birth weight (kg), mean ± SD, N=130	3.11 ± 0.72
History of perinatal stress, % (n), N=123	43% (53)
Past Medical History, % (n)	
Genetic Disorder	5.5% (8)
Neurodevelopment Disorder	16% (23)
Cardiac Disease	6.2% (9)
Pulmonary Disease	9.7% (14)
Gastroenterology Disease	20% (29)
Other	15% (22)
Weight-for-age percentile, median (IQR), N=140	29.5 (11.5, 58.1)
Height-for-age percentile, median (IQR), N=141	25.0 (8.3, 57.0)
Weight status category, % (n), N=140	
Underweight	13% (18)
Normal	71% (100)
Overweight	11% (16)
Obese	4.3% (6)
Prior history of hypoglycemia, % (n)	20% (29)
Presenting illness features, % (n)	
Gastroenteritis	25% (36)
Vomiting	44% (64)
Diarrhea	14% (20)
Upper respiratory tract infection	22% (32)
Otitis media	2.8% (4)
Fever	30% (44)
Other	12% (18)
Illness duration (days), median (IQR), N=123	2 (1, 4)
History of decreased oral intake (days), median (IQR), N=78	2 (1, 3)
Symptomatic hypoglycemia at presentation, % (n)	64% (93)

353 *unless otherwise noted

354

355 **Table 2. Characteristics of patients in whom an underlying etiology for hypoglycemia was**
356 **identified versus those without a diagnosis**

Variable N=145*	Diagnosis established N=12	No diagnosis established N=133	p-value
Age at presentation (years), median (IQR)	1.03 (0.05, 1.54)	2.18 (1.29, 3.99)	<0.001†
Sex, % female (n)	67% (8)	54% (72)	0.55‡
Race, % White (n)	75% (9)	60% (81)	0.54‡
Ethnicity, % Hispanic (n)	0% (0)	2.3% (3)	>0.99‡
Weight-for-age percentile, median (IQR), N=140	13.1 (1.7, 23.8)	31.0 (14.0, 59.5)	0.02†
Height-for-age percentile, median (IQR), N=141	15.5 (5.6, 23.3)	29.0 (9.0, 59.0)	0.10†
Weight status category, % (n), N=140			0.27‡
Underweight	17% (2)	13% (16)	
Normal	83% (10)	70% (90)	
Overweight/Obese	0% (0)	17% (22)	
Prior history of hypoglycemia, % (n)	25% (3)	20% (26)	0.71‡
Past medical/surgical history, % (n)	17% (2)	50% (67)	0.03‡
Abnormal physical examination findings, % (n)	8.3% (1)	5.3% (7)	0.51‡
Presenting illness features, % (n)			
Gastroenteritis	25% (3)	25% (33)	>0.99‡
Vomiting	25% (3)	46% (61)	0.23‡
Diarrhea	25% (3)	13% (17)	0.22‡
Upper respiratory tract infection	17% (2)	23% (30)	>0.99‡
Otitis media	0% (0)	3.0% (4)	>0.99‡
Fever	33% (4)	30% (40)	0.76‡
Other	17% (2)	12% (16)	0.65‡
Illness duration (days), median (IQR), N=123	2 (1, 6)	2 (1, 4)	0.82†
History of decreased oral intake (days), median (IQR), N=78	3.5 (1, 6)	2 (1, 3)	0.47†
Symptomatic hypoglycemia at presentation, % (n)	50% (6)	65.4% (87)	0.35‡
Autonomic symptoms	0% (0)	6.0% (8)	>0.99‡
Neuroglycopenic symptoms	50% (6)	63% (84)	0.37‡
Labs at initial presentation			
Plasma glucose (mmol/L [mg/dL]), median (IQR)	2.5 (1.4, 2.7) [45 (26, 49)]	2.5 (2.1, 2.9) [45 (37, 52)]	0.42†
Plasma glucose <2.8 mmol/L (<50 mg/dL), % (n)	83% (10)	69% (92)	0.51‡
Positive plasma or urine ketones, % (n), N=82	25% (1)	92% (72)	0.004‡
Serum bicarbonate (mmol/L), mean ± SD, N=91	22 ± 5.5	16 ± 3.6	<0.001§
Other abnormal findings on presenting or baseline evaluation,‖ % (n), N=111	25% (2)	44% (45)	0.46‡

357 *unless otherwise noted, †Wilcoxon rank sum test, ‡Fisher's exact test, §t-test, ‖including transaminases, lactate, ammonia,
358 cortisol, growth hormone, IGF-I, IGFBP-3, acylcarnitine profile, carnitine profile, urine organic acids
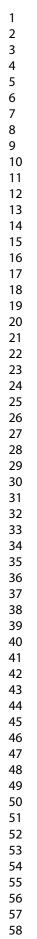
359

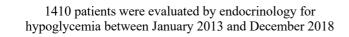360 **Table 3. Factors associated with performing diagnostic fast**

Variable N=145*	Diagnostic fast N=69	No diagnostic fast N=76	p-value
Age at presentation (years), median (IQR)	1.94 (1.23, 3.60)	2.12 (1.20, 3.96)	0.51†
Sex, % female (n)	62% (43)	49% (37)	0.13‡
Race, % White (n)	68% (47)	57% (43)	0.17‡
Ethnicity, % Hispanic (n)	0% (0)	3.9% (3)	0.25‡
Weight-for-age percentile, median (IQR), N=140	29.2 (10.5, 59.5)	30.5 (14.0, 54.5)	0.61†
Height-for-age percentile, median (IQR), N=141	22.0 (7.2, 55.0)	29.3 (9.0, 60.0)	0.55†
Weight status category, % (n), N=140			0.68‡
Underweight	15% (10)	11% (8)	
Normal	74% (50)	72% (52)	
Overweight/Obese	12% (8)	17% (12)	
Prior history of hypoglycemia, % (n)	23% (16)	17% (13)	0.41‡
Past medical/surgical history, % (n)	42% (29)	53% (40)	0.25‡
Abnormal physical examination findings, % (n)	5.8% (4)	5.3% (4)	>0.99‡
Presenting illness features, % (n)			
Gastroenteritis	29% (20)	21% (16)	0.34‡
Vomiting	36% (25)	51% (39)	0.09‡
Diarrhea	17% (12)	11% (8)	0.34‡
Upper respiratory tract infection	25% (17)	20% (15)	0.55‡
Otitis media	1.5% (1)	4.0% (3)	0.62‡
Fever	30% (21)	30% (23)	>0.99‡
Other	15% (10)	11% (8)	0.62‡
Illness duration (days), median (IQR), N=123	2 (1, 5)	2 (1, 4)	0.58†
History of decreased oral intake (days), median (IQR), N=78	2 (1, 3)	2 (1, 3)	0.73†
Symptomatic hypoglycemia at presentation, % (n)	71% (49)	58% (44)	0.12‡
Autonomic symptoms	4.4% (3)	6.6% (5)	0.72‡
Neuroglycopenic symptoms	70% (48)	55% (42)	0.09‡
Labs at initial presentation			
Plasma glucose (mmol/L [mg/dL]), median (IQR)	2.2 (1.8, 2.7) [40 (32, 49)]	2.6 (2.3, 3.0) [47 (41, 55)]	0.002†
Plasma glucose <2.8 mmol/L (<50 mg/dL), % (n)	80% (55)	62% (47)	0.03‡
Positive plasma or urine ketones, % (n), N=82	83% (29)	94% (44)	0.16‡
Serum bicarbonate (mmol/L), mean ± SD, N=91	17 ± 4.0	16 ± 4.0	0.26§
Other abnormal findings on presenting or baseline evaluation,‖ % (n), N=111	38% (22)	47% (25)	0.34‡

361
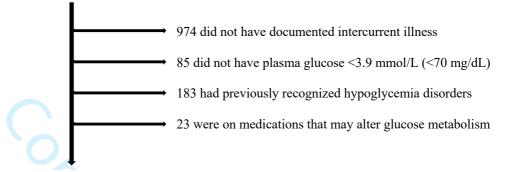362 *unless otherwise noted, †Wilcoxon rank sum test, ‡Fisher's exact test, §t-test, ‖including transaminases, lactate, ammonia, cortisol, growth hormone, IGF-I, IGFBP-3, acylcarnitine profile, carnitine profile, urine organic acids

363   **Figures and Figure Legends**

364   **Figure 1. Consort diagram**

1410 patients were evaluated by endocrinology for
hypoglycemia between January 2013 and December 2018

→ 974 did not have documented intercurrent illness

→ 85 did not have plasma glucose <3.9 mmol/L (<70 mg/dL)

→ 183 had previously recognized hypoglycemia disorders

→ 23 were on medications that may alter glucose metabolism

145 patients included in analysis

Supplemental Table 1. Details of genetic testing performed

Of the genetic testing conducted, a commercial panel testing for glycogen storage diseases (sequencing of *AGL, G6PC, GAA, GBE1, GYS2, PFKM, PHKA1, PHKA2, PHKB, PHKG2, PYGL, PYGM, SLC2A2*, and *SLC37A4*) was obtained most frequently, in 14 patients. A ketotic hypoglycemia panel (sequencing and deletion/duplication analysis of *ACAT1, AGL, G6PC, GYS2, PHKA2, PHKB, PHKG2, PYGL, SLC16A1*, and *SLC37A4*) was obtained in 10 patients, hyperinsulinism panel (including sequencing of *ABCC8, KCNJ11, GCK, GLUD1* in all cases, with the addition of sequencing and deletion/duplication analysis of *ABCC8, KCNJ11, GLUD1, HADH, HNF1A, HNF4A, INSR, SLC16A1, UCP2* depending on the panel utilized) was obtained in six patients, fatty acid oxidation defect panel (sequencing and deletion/duplication analysis of *ACADVL*) was obtained in five patients, isolated *SLC16A1* mutation analysis was performed in three patients, and one patient had a commercial metabolic hypoglycemia panel (sequencing of *ACAT1, AGL, ALDOB, FBP1, G6PC, GALT, GYS2, HMGCL, MLYCD, OXCT1, PC, PCK1, PCK2, PGM1, PHKA2, PHKB, PHKG2, PYGL, SLC16A1, SLC2A2*, and *SLC37A4*) obtained. One child had targeted testing for Russel Silver syndrome based upon clinical examination findings. Chromosomal microarray was obtained in one patient and four patients had whole exome sequencing.

Supplemental Table 2. Summary of patients with identified hypoglycemia diagnoses

History and initial presentation	Evaluation findings	Treatment and course
Growth hormone deficiency		
Term male, history of uninvestigated neonatal hypoglycemia. Presented at 10 months with vomiting, irritability, and POC PG of 32 mg/dL. Length z score -2.24, weight-for-length 80%ile.	Ketotic hypoglycemia (PG 52 mg/dL, BOHB 2.3 mmol/L) with normal lactate and cortisol (20 mcg/dL) but low GH 0.97 ng/mL. Peak GH after stimulation (arginine/clonidine) was 9.7 ng/mL and MRI revealed a small pituitary gland with possible ectopic pituitary tissue.	Initiated GH with resolution of hypoglycemia. Remains on GH replacement at 9 years of age.
Fatty acid oxidation disorder		
23-month-old female without significant past medical history presented with seizure and POC PG 20 mg/dL in setting of gastroenteritis.	Hypoketotic hypoglycemia with hyperfattyacidemia (PG 39 mg/dL, BOHB 1.4 mmol/L, FFA 3.98 mmol/L). Acylcarnitine profile revealed mild increase of C14:1 and C14:2 and UOA showed markedly increased dicarboxylic acids. Sequencing of *ACADVL* was negative, however, fatty acid oxidation probe of fibroblasts demonstrated significantly reduced oxidation of palmitate, consistent with impaired long-chain fatty acid oxidation.	Dextrose-containing fluids every 2 hours with illness. Multiple additional episodes of hypoglycemia during illness, one requiring hospitalization.
Dihydrolipoamide dehydrogenase (DLD) deficiency		
14-month-old male without significant medical history presented with gastroenteritis, lethargy, seizures, and PG 9 mg/dL.	Hypoglycemia with lactic acidosis and abnormal urine organic acid profile (PG 40 mg/dL, BOHB 1.3 mmol/L, FFA 2.5 mmol/L, lactate 5.2 mmol/L, ammonia 18 µmol/L, UOA: increased lactate, ketone, 2OH-glutaric acid, TCA cycle intermediates, 2-keto-glutaric acid, 2OH-adipic acid and glutaric acid). WES identified compound heterozygous variants in *DLD* Gly229Cys / Ser258Pro.	Low-protein diet. Numerous admissions for hypoglycemia and intermittent hepatic dysfunction.
3 methylcrotonyl-CoA carboxylase deficiency		
18-month-old female without significant past medical history presented with vomiting, lethargy, PG 49 mg/dL, and HCO3 16 mmol/L.	Ketotic hypoglycemia with abnormal urine organic acid profile (PG 52 mg/dL, BOHB 3.9 mmol/L, lactate 1.2 mmol/L, ammonia <9 µmol/L, acylcarnitine profile: moderate increase of C5OH-carnitine, UOA: increased 3-methylcrotonylglycine, lactic acid, 3-hydroxy-isovalerate, consistent with deficiency in 3 methylcrotonyl-CoA carboxylase. *MCCC1* sequencing identified a heterozygous novel pathogenic frameshift variant (Ser622Pro).	Limit fasting. Glucose meter and ketone meter monitoring. Multiple episodes of ketosis during illness, all managed at home.
Hyperinsulinism		
Term female born AGA, limited prenatal care. Presented at 5 days of age with jaundice and diarrhea due to rotavirus. POC PG 49 mg/dL, HCO3 23 mmol/L.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon on fast at 11 days of age (PG 57 mg/dL, BOHB 1.2 mmol/L, FFA 1.04 mmol/L, insulin <2 µIU/mL, C-peptide 0.22 ng/mL, IGFBP-1 167 ng/mL, ammonia 27 µmol/L, cortisol 25 mcg/dL, GH 10.3 ng/mL, Δ PG +45 mg/dl post-glucagon). Fasted 12 hours with PG >70 mg/dL. Genetic testing not performed. Presumed PSI-HI.	Diazoxide not initiated given fasting tolerance. Glucagon PRN, glucose meter monitoring. At 7 months of age, no PG <70 mg/dL on home monitoring.
Term female born AGA to GBS+ mother. Presented at 4 days of age with fever, irritability, POC PG 36 mg/dL, and HCO3 14 mg/dL. Infectious work-up was negative.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon on fast at 14 days of age (PG 43mg/dL, BOHB 0.8 mmol/L, FFA 0.8 mmol/L, insulin <2 µIU/mL, C-peptide 0.16 ng/mL, IGFBP-1 144 ng/mL, ammonia 39 µmol /L, cortisol 17 mcg/dL, GH 18 ng/mL, Δ PG +40 mg/dl post-glucagon). Fasted 8 hours with PG >70 mg/dL. Sequencing of *ABCC8*, *KCNJ11*, *GCK*, and *GLUD1* identified VUS in *GLUD1* (Ala49Thr).	Diazoxide not initiated given fasting tolerance. Limit fasting to 8 hours, glucagon PRN, glucose meter monitoring. Lost to follow-up.
Term male born SGA, history of uninvestigated neonatal hypoglycemia. Presented at 1 month of age with	Hypoketotic hypoglycemia with hypofattyacidemia (PG 50 mg/dL, BOHB 0.62 mmol/L, FFA 0.57 mmol/L, insulin <2 µIU/mL, C-peptide 0.21 ng/mL, lactate 0.8 mmol/L, ammonia 32 µmol/L, cortisol 10 mcg/dL, GH 4.08 ng/mL, glucagon stimulation not performed). Fasted 11	Glucagon PRN, glucose meter. Repeat fast at age 9 months demonstrated resolution of HI

fever, POC PG 58 mg/dL, and POC BOHB <0.3 mmol/L. + parechovirus.	hours with PG >70 mg/dL. Sequencing and del/dup of *ABCC8*, *KCNJ11* and sequencing of *GCK*, *GLUD1*, *HADH*, *HNF1A*, *HNF4A*, *SLC16A1*, and *UCP2* was negative.	(PG 42 mg/dL, BOHB 2.4 mmol/L, IGFBP-1 723 ng/mL).
Term male infant born with AGA. Presented at 2 days with diarrhea, irritability, and POC PG 49 mg/dL. Required max GIR 13 mg/kg/min. Found to have shigella enteritis.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon on fast at 8 days of age (PG 44 mg/dL, BOHB 0.9, FFA 0.72 mmol/L, insulin <2 µIU/mL, C-peptide 0.22 ng/mL, lactate 1.3 mmol/L, ammonia 19 µmol/L, cortisol 6 mcg/dl, GH 4.84 ng/mL, Δ PG +30 mg/dl post-glucagon). Fasted <3 hours with PG >70 mg/dL. Sequencing and del/dup of *ABCC8, KCNJ11, GLUD1, HADH, HNF1A, HNF4A, INSR, SLC16A1,* and *UCP2* and sequencing of *GCK* was negative.	Diazoxide 5 mg/kg/d, glucagon PRN, glucose meter monitoring. Transferred care to local endocrinologist at discharge.
Term female born AGA with failure to thrive and GERD. Presented at 5 months of age with fever, congestion, seizure, POC PG 42 mg/dL, HCO3 24 mmol/L, and negative urine ketones.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon (PG 42 mg/dL, BOHB <0.3 mmol/L, FFA 0.19 mmol/L, insulin <2 µIU/mL, C-peptide 0.35 ng/mL, lactate 1.3 mmol/L, ammonia 33 µmol/L, cortisol 11.6 mcg/dl, GH 8.07 ng/mL, Δ PG +45 mg/dl post-glucagon). Fasted <3 hours with PG >70 mg/dL. Sequencing and del/dup of *ABCC8, KCNJ11, GLUD1, HADH, HNF1A, HNF4A, INSR, SLC16A1,* and *UCP2* and sequencing *GCK* was negative for genes analyzed, revealed partial deletion of X chromosome, cytogenic analysis subsequently confirmed mosaicism for monosomy X and ring X confirming a diagnosis of Turner syndrome.	Enteral dextrose via G-tube. Later started lanreotide. At age 5 years, repeat fast off therapy demonstrated a safe fasting tolerance (PG >70 for 12 hours) but continued evidence of HI.
Female born at 34 weeks, SGA with heterotaxy syndrome. Presented at 18 months with fever, URI, diarrhea, POC PG 54 mg/dL, HCO3 28 mmol/L, and negative urine ketones.	Hypoketotic hypoglycemia with glycemic response to glucagon (PG 50 mg/dL, BOHB 1.7 mmol/L, FFA 2.1 mmol/L, insulin <2 µIU/mL, C-peptide 0.3 ng/mL, lactate 1.8 mmol/L, ammonia <9 µmol/L, cortisol 8.5 mcg/dL, GH 1.6 ng/mL, Δ PG >30 mg/dl post-glucagon). Fasted 3 hours with PG >70 mg/dL. Sequencing and del/dup of *ABCC8, KCNJ11, GLUD1, HADH, HNF1A, HNF4A, INSR, SLC16A1,* and *UCP2* and sequencing of *GCK* was negative.	Enteral dextrose via G-tube. Required treatment through age 3 years when demonstrated ability to fast 18 hours with PG >70 mg/dL off treatment.
Term female with history of uninvestigated neonatal hypoglycemia. Presented at 18 months with gastroenteritis and POC PG 16 mg/dL.	Hypoketotic hypoglycemia with hypofattyacidemia and glycemic response to glucagon (PG 45mg/dL, BOHB 0.62 mmol/L, FFA 0.5 mmol/L, insulin < 1 µIU/mL, C-peptide 0.5 ng/mL, lactate 1.2 mmol/L, ammonia 33 µmol/L, cortisol 5.1 mcg/dL, Δ PG + 68 mg/dl post-glucagon). Sequencing and del/dup of *ABCC8*, *KCNJ11* and sequencing of *GCK* and *GLUD1* identified an autosomal dominant paternally inherited mutation in *ABCC8* (pSer1387del)	Enteral dextrose via G-tube and lanreotide. Overnight enteral dextrose discontinued by 3 years of age. Remains on lanreotide.
Impaired hepatic insulin clearance		
22-month-old female with fever, URI, gastroenteritis, PG 48 mg/dl, HCO3 25 mmol/L, AST 6774 U/L, ALT 4847 U/L, and prolonged PT and PTT. Diagnosed with acute hepatic insufficiency due to rhinovirus and enterovirus. Hypoglycemia persisted despite improved liver function.	Hypoketotic hypoglycemia with elevated insulin and appropriately low C-peptide (PG 50 mg/dL, BOHB <0.3 mmol/L, FFA 2.0 mmol/L, insulin 8.6 µIU/mL, C-peptide 0.3 ng/mL, lactate 2.0 mmol/L, ammonia 32 µmol/L, cortisol 18.6 mcg/dL, GH 1.53 ng/mL, no glycemic response to glucagon, normal acylcarnitine profile and UOA). Fasting study repeated x 3 with consistent results.	Enteral dextrose via NG-tube overnight. Discontinued at 26 months of age following repeat fast demonstrating resolution of inappropriate insulin action (PG 47 mg/dL, BOHB 3.0 mmol/L, FFA 3.46 mmol/L, insulin <2 µIU/mL, and C-peptide < 0.1 ng/mL).

AGA appropriate for gestational age, ALT alanine aminotransferase, AST aspartate aminotransferase, BOHB ß-hydroxybutyrate, FFA free fatty acids, GBS Group B *Streptococcus*, GERD gastroesophageal reflux disease, GH growth hormone, GIR glucose infusion rate, G-tube gastrostomy tube, HCO3 bicarbonate, HI hyperinsulinism, IGFBP-1 insulin-like growth factor binding protein 1, MRI magnetic resonance imaging, NG nasogastric tube, PG plasma glucose, POC point-of-care, PRN *pro re nata*, PSI-HI perinatal stress induced hyperinsulinism, PT prothrombin time, PTT partial thromboplastin time, SGA small for gestational age, TCA tricarboxylic acid cycle, UOA urine organic acids, URI upper respiratory infection, WES whole exome sequencing