

## Frequency of Hypoglycemia During Insulin Tolerance Test in Children with Suspected Growth Hormone Deficiency

DR. JAVAID ZAFFAR, MBBS  
NISHTAR HOSPITAL, MULTAN.

DR. SUNDAS RAMZAN, MBBS  
NISHTAR HOSPITAL, MULTAN.

DR. SOBIA MAZHAR, MBBS  
NISHTAR HOSPITAL, MULTAN.

### Abstract

**OBJECTIVE:** To determine the frequency of hypoglycemia during insulin tolerance test in children with suspected growth hormone deficiency. **Material and Methods:** A total of 62 short stature children suspected of growth hormone deficiency were enrolled from department of pediatric medicine, Nishtar Hospital, Multan using non-probability consecutive sampling technique. Total duration was 1 year from May 2016 to May 2017. These children underwent insulin tolerance test and were examined for the development of hypoglycemia at different time intervals. All the data were recorded on the proforma. Data were entered and analyzed using SPSS-18. **Results:** Of these 62 study cases, 36 (58.1%) were boys and 26 (41.9%) were girls. Mean age of our study cases was  $8.94 \pm 2.81$  (Minimum age was 4 years while maximum age was 13 years) and majority of study cases i.e. 37 (59.7%) belonged to age group of 4 – 9 years of age. Mean height of our study cases was  $107.81 \pm 12.67$  centimeters (Minimum height 80 cm while maximum height was 130 cm), majority of study cases i.e. 53 (85.5%) of our study cases had height in the range of 80 – 120 cm. Mean weight of the study cases was  $17.00 \pm 5.66$  kilograms (Minimum weight was 6 Kg while maximum weight was 35 Kg), majority of our study cases i.e. 51 (82.3%) were having weight in the range of 6-20 Kg. Mean values for baseline blood glucose level were  $92.27 \pm 10.99$  mg/dl (Minimum baseline blood glucose level was 55 mg/dl while maximum value was 111 mg/dl). Mean first blood glucose level after 30 minutes of administration of Insulin was  $46.56 \pm 14.07$  mg/dl, after 45 minutes was  $47.26 \pm 9.45$  mg/dl, after 60 minutes was  $61.35 \pm 17.63$  mg/dl, after 90 minutes was  $69.44 \pm 16.17$  mg/dl, after 120 minutes was  $79.65 \pm 12.18$  mg/dl. Hypoglycemia was seen in 49 (79%) of our study cases (Table-6). Growth hormone deficiency was observed in 39 (62.90%), 23 (37.10 %) were normal cases. **Conclusion:** Insulin tolerance test (ITT) is safe and reliable test, if being performed in compliance with standard protocols under appropriate supervision of trained healthcare professionals for proper monitoring of side effects. The test should only be performed in the centers having well trained and qualified staff and proper equipment to treat any possible side effect.

**Keywords:** Hypoglycemia, Growth hormone deficiency, Short stature.

### Introduction

Short stature is a commonly occurring problem all over the world particularly in children of developing countries. It is defined as height or length below 3<sup>rd</sup> percentiles for the particular age and gender.<sup>1</sup> It can be physiological; positive family history, constitutional delayed growth and poor dietary habits or pathological; endocrinopathies (hypothyroidism, growth hormone deficiency, cushing's syndrome), malnutrition and chronic childhood diseases<sup>2</sup>.

Growth hormone (GH) is involved in stimulation of growth, cellular reproduction and regeneration and it is a protein-based peptide hormone, synthesized by the pituitary glands.<sup>3</sup> Growth hormone deficiency (GHD) means the pituitary gland does not make enough growth hormone. The exact magnitude of growth hormone deficiency in children is not known; different studies have shown its occurrence varying from 1 out of 4,000 to 1 per 10,000 cases presenting with childhood short stature.<sup>4</sup> The exact magnitude of growth hormone deficiency in Pakistan is also not known, however few local studies in children presenting with short stature have shown it ranging from 6.1% to 14%.<sup>5,6</sup>

In GHD the child presents with short stature, growth retardation and delayed puberty and about 5% of children suffering from growth hormone deficiency may also have episodes of hypoglycemia.<sup>7</sup>

The diagnosis of GHD in children is a challenging task, requiring both clinical and laboratory investigations. Insulin tolerance test (ITT) is known as gold standard for evaluation of the functional stability of the hypothalamo-pituitary-adrenal axis among children.<sup>8,9</sup> The ITT is safe when it is performed in children following strictly international protocols in healthcare facilities having mechanism for monitoring of any adverse event.<sup>10,11</sup> Hypoglycemia (symptomatic/asymptomatic) is observed in GHD patients during ITT. In a study done at Department of pediatrics, National Institute of Child Health, Aga Khan University Hospital, Karachi the

incidence of hypoglycemia was 79.8%.<sup>10</sup>

Earlier no such study has been done in this region, so this study may help in estimating the proportion of patients developing this complication and anticipating the management plan.

### Material and Methods

Short stature patients suspected of growth hormone deficiency presenting in the Department of Pediatric Medicine, Nisthar Hospital, Multan and meeting the inclusion criteria (having height or length below 3<sup>rd</sup> percentile for age and, short statured patients 4-14 years of age with either gender suspected of having GHD) were included in the study. Patients having weight <10 kg, Epilepsy or hypoglycemic fits, type 1 DM (RBS >200mg/dl), hypothyroidism, Addison's disease or panhypopituitarism, Cardiac disease, deranged RFT (creatinine >1.2g/dl) were excluded from our study. All the details including risks/benefits of the study were discussed with the parents/guardians of all the children and an informed written consent was taken. Their demographic details (name, age, gender, contact) was noted. The ITT was carried out in the presence of a doctor and trained staff nurse. The baseline blood glucose level was checked with glucometer and rapid acting insulin was given at a dose of 0.1IU/kg i/v. Blood samples for serum blood glucose and serum GH were drawn at 0, 30, 45, 60, 90 and 120 minutes and were sent to the laboratory, all the blood glucose levels during ITT were checked on glucometer as well.

Intravenous 10% dextrose water was kept ready in syringe for immediate infusion if patient develops hypoglycemic symptoms (sweating, palpitations, lack of concentration) and rarely seizures and loss of consciousness. Following the test the child was provided a meal and discharged from the hospital only when he maintained blood glucose level above 72mg/dL. Data were entered & analyzed by using SPSS version 20.0. Mean and standard deviation was calculated for quantitative variables like age. Qualitative variables like gender and proportion of hypoglycemic patients have been presented as frequencies and percentages. Outcome was frequency of hypoglycemia that is total number of patients in test having hypoglycemia. **Hypoglycemia:** It was defined as blood glucose <45 mg/dl at any time during insulin tolerance test. **Growth hormone deficiency:** It was defined as the value of peak serum growth hormone less than 10 ug/l.

### Results

Short stature patients suspected of growth hormone deficiency meeting inclusion criteria of our study were included. A total of 62 study cases were enrolled. Of these 62 study cases, 36 (58.1%) were boys and 26 (41.9%) were girls. Mean age of our study cases was  $8.94 \pm 2.81$  and 37 (59.7%) belonged to age group of 4 – 9 years of age. Mean height of our study cases was  $107.81 \pm 12.67$  centimeters (Minimum height 80 cm while maximum height was 130 cm), majority of study cases i.e. 53 (85.5%) of our study cases had height in the range of 80 – 120 cm. Mean weight of the study cases was  $17.00 \pm 5.66$  kilograms (Minimum weight was 6 Kg while maximum weight was 35 Kg), majority of our study cases i.e. 51 (82.3%) were having weight in the range of 6-20 Kg. Mean values for baseline blood glucose level were  $92.27 \pm 10.99$  mg/dl (Minimum baseline blood glucose level was 55 mg/dl while maximum value was 111 mg/dl). Mean first blood glucose level after 30 minutes of administration of Insulin was  $46.56 \pm 14.07$  mg/dl, after 45 minutes was  $47.26 \pm 9.45$  mg/dl, after 60 minutes was  $61.35 \pm 17.63$  mg/dl, after 90 minutes was  $69.44 \pm 16.17$  mg/dl, after 120 minutes was  $79.65 \pm 12.18$  mg/dl. Hypoglycemia was seen in 49 (79%) of our study cases. Growth hormone deficiency was observed in 39 (62.90%), 23 (37.10 %) were normal cases.

### Discussion

Childhood short stature puts significant amount of psychological stress and cause of concern for the suffering families particularly among parents and suffering child. Childhood short stature leads to negative impact on physical activity like sports and their educational performance in schools. Among the common causes of the childhood short stature include family history of short stature, poor dietary habits including malnutrition, thyroid dysfunction, chronic illnesses, psychosocial dwarfism, certain genetic disorders and growth hormones deficiencies. among children and their parents<sup>12,13</sup>. In patients presenting with short stature growth hormone deficiency is suspected where other features relating to poor growth have not been found<sup>14,15</sup>.

Short stature patients suspected of growth hormone deficiency meeting inclusion criteria of our study were included. A total of 62 study cases were enrolled. Of these 62 study cases, 36 (58.1%) were boys and 26 (41.9%) were girls. Similar findings have been reported by Al-Ruhaily et al<sup>16</sup>, who reported 63.33% versus 36.67 % respectively. Lone et al<sup>8</sup> reported 58 % males and 42 % female patients.

Mean age of our study cases was  $8.94 \pm 2.81$  (Minimum age was 4 years while maximum age was 13 years) and majority of study cases i.e. 37 (59.7%) belonged to age group of 4 – 9 years of age. Lone et al<sup>8</sup> reported  $10 \pm 3.5$  years mean age in their study, their results are close to that of ours. Al-Ruhaily et al<sup>16</sup> reported  $14.6 \pm 1.6$  years, which are higher than that of our ages of our study cases because of the fact that our inclusion criteria was restricted to only 4-14 years of age so our age are a bit lower than Al-Ruhaily et al<sup>16</sup>.

Mean height of our study cases was  $107.81 \pm 12.67$  centimeters (Minimum height 80 cm while maximum height was 130 cm), majority of study cases i.e. 53 (85.5%) of our study cases had height in the range of 80 – 120 cm. Al-Ruhaliy et al<sup>16</sup> reported mean height of study cases as  $139.7 \pm 7.6$  centimeters, these differences in the heights of study cases can be described in terms of the fact that their study cases had increased mean age than ours.

Mean weight of the study cases was  $17.00 \pm 5.66$  kilograms (Minimum weight was 6 Kg while maximum weight was 35 Kg), majority of our study cases i.e. 51 (82.3%) were having weight in the range of 6-20 Kg. Al-Ruhaily et al<sup>16</sup> reported mean weight of their study cases as  $37.4 \pm 9.9$  kg. Again this value is higher than that ours due to higher age groups being included in their study.

Mean values for baseline blood glucose level were  $92.27 \pm 10.99$  mg/dl (Minimum baseline blood glucose level was 55 mg/dl while maximum value was 111 mg/dl). Mean first blood glucose level after 30 minutes of administration of Insulin was  $46.56 \pm 14.07$  mg/dl, after 45 minutes was  $47.26 \pm 9.45$  mg/dl, after 60 minutes was  $61.35 \pm 17.63$  mg/dl, after 90 minutes was  $69.44 \pm 16.17$  mg/dl, after 120 minutes was  $79.65 \pm 12.18$  mg/dl. Maximum number of our study cases i.e. 58.06 % developed hypoglycemia within 30 minutes of test. Lone et al<sup>8</sup> reported the same but their frequency was less than ours (35%).

In literature various rates of hypoglycemia have been reported. Hypoglycemia was seen in 49 (79%) of our study cases. A study conducted by Jaruratanasirikul et al<sup>17</sup> reported 100 % frequency of hypoglycemia in children undergoing Insulin tolerance test between 15 – 45 minutes which are higher rates than our frequency (79%). A study conducted by Lone et al<sup>8</sup> reported 79.8 % children with hypoglycemia in children undergoing Insulin tolerance test.

Growth hormone deficiency was observed in 39 (62.90%), 23 (37.10 %) were normal cases. A study conducted by Awan et al<sup>5</sup> reported 14 % frequency of growth hormone deficiency among short stature children while lone et al<sup>8</sup> reported 66% frequency of GHD.

All these study cases were monitored for any side effects event effects /adverse events and none of these children developed adverse complications of hypoglycemia such as seizures, loss of consciousness / drowsiness or hypothermia  $<35^{\circ}\text{C}$ . None of these study cases required intravenous glucose administration after having hypoglycemia. All the children successfully completed this test without having any serious side effects.

## Conclusion

Insulin tolerance test (ITT) is safe and reliable test, if being performed in compliance with standard protocols under appropriate supervision of trained healthcare professionals for proper monitoring of side effects. The test should only be performed in the centers having well trained and qualified staff and proper equipment to treat any possible side effect. Higher frequencies of hypoglycemia were observed in our study.

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