# ORIGINAL ARTICLE

## Visual Perception in Children with a History of Hypoglycemia due to Hyperinsulinism

**How to Cite This Article:** Ghazavi MR, Nasiri J, Momeni A . Visual Perception in Children with a History of Hypoglycemia due to Hyperinsulinism. Iran J Child Neurol. Winter 2024; 18(1) :17-24

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## Abstract

### Objectives

Hyperinsulinism refers to improper insulin secretion in the presence of low plasma glucose, causing severe and persistent hypoglycemia in infants and children. The brain's occipital lobe, which includes the visual and plays an essential role in visual perception is specifically sensitive to hypoglycemia-induced damage. The present study aims to investigate the visual perception in children suffering from hyperinsulinism and to compare it with the control group.

### Materials & Methods

This cross-sectional control study, conducted in 2020 in Isfahan, Iran, involved 20 children aged 4-13 years with hyperinsulinism and 20 healthy children of the same age and gender for comparison. In both groups, the measuring instrument was the Test of Visual Perceptual Skills (non-motor) Third Edition.

### Results

The mean visual perceptual quotient in the case and control groups was 80.50±26.74 and 116.50±7.56 (p-value<0.001), respectively. The results overall indicated that children suffering from hyperinsulinism were weaker than healthy children in all areas of visual perception.

### Conclusion

Based on the obtained results, it is recommended that children suffering from hyperinsulinism be screened regarding visual perceptual disorders since this screening may be helpful in initiating different rehabilitation programs among these patients.

Received: 20 -Apr-2021
Accepted: 25- Jan-2022
Published: 18-Jan-2024

**Keywords:** Hyperinsulinism, Hypoglycemia, Occipital Lobe, Visual Perception
**DOI:** 10.22037/ijcn.v18i1.34620

## Introduction

Hyperinsulinism refers to improper insulin secretion in the presence of low plasma glucose, resulting in severe and persistent hypoglycemia in infants and children (1) .

In hyperinsulinism, due to the suppressive effect of insulin on lipolysis and ketogenesis, the level of ketone bodies in the presence of hypoglycemia remains low, causing a high risk of brain damage resulting from hypoglycemia in these patients(2).

Hyperinsulinism is the most common cause of persistent hypoglycemia in early infancy. The onset of disease varies from childbirth up to 18 months of age, but sometimes, it manifests itself for the first time in older children(3) .

Severe hypoglycemia is associated with brain lesions and abnormal neurodevelopment. It also damages the occipital and parietal cortex plus the subcortical white matter (4,5).

The effect of hypoglycemia on vision is essential since the occipital lobe of the brain, including the visual cortex, is specifically sensitive to the damage induced by hypoglycemia(6). Visual perception relies on the health of the posterior visual pathway, as well as the cortical network springing from the occipital lobe(7).

Visual perception refers to the ability to observe and interpret (analyze and give meaning) visual information around us. The visual perception skills include several significant areas:

- Visual discrimination
- Visual memory
- Visual spatial relationships
- Visual form constancy
- Visual sequential memory
- Visual figure-ground discrimination
- Visual closure (8)

When visual information is not processed or appropriately perceived, it cannot be coordinated or integrated with other senses. Meanwhile, interrelationships exist between visual perception skills, reading, employment, and social interactions. For all these tasks, the person should be able to process visual stimuli well (9).

The Test of Visual Perception Skills (Non-Motor) Third Edition (TVPS-3) is a widely used assessment tool designed to evaluate visual perception in children across seven key areas. Initially developed by Nancy A. Martin in 2006, this instrument is an essential resource for professionals looking to gauge visual perception levels in a pediatric population (10).

This test is not a test that measures a subject's sight or vision; only a subject's ability to interpret what the subject sees. However, a defect in sight or vision could distort what the subject sees, consequently having some effect on a subject's performance on the TVPS-3. If a sight or vision impairment interferes with the subject making an accurate visual-perceptual interpretation, the subject should be referred to an optometrist or an ophthalmologist(11).

Concerning the critical role of visual perception

skills in daily activities, as well as the training programs of children alongside the sparse research performed so far in this area on patients suffering hyperinsulinism, the researchers decided to first evaluate the visual perception skills in this group of patients using TVPS-3 test and then compare them with the normal control group.

## Materials & Methods

The target population consists of children with hyperinsulinism with 4-13 years of age (20 cases), referring to the Pediatric Endocrine Clinic of Isfahan, Iran in 2020.

The control group also consisted of healthy 4-13-year-old children referring to pediatric clinic (20 cases) ; they were chosen such that they would match those with hyperinsulinism in terms of age and gender.

All patients met the hyperinsulinism diagnostic criteria based on critical samples taken during hypoglycemia (plasma glucose less than 50 mg/dl). These criteria included:

1- Hyperinsulinemia (insulin concentration > 2 microunit/ml)

2. Fatty acid deficiency (plasma-free fatty acids < 1.5 mmol/L)

3. Hypoketonemia (beta- hydroxybutyrate< 2 mmol/L)

4. Abnormal glycemic response to intravenous glucagon by 1 mg (glucose elevation beyond 40 mg/dL)

As with other criteria, none of the children had visual deficiency or refractive errors not resolvable by glasses. They should not have vision disorders due to other specific causes, including congenital glaucoma, Rop,Torch, ocular trauma, and ocular infections damaging the vision.

### Measuring instruments

The measurement instrument was the third edition of the Visual Perceptual Skills Test (TVPS-3)

This test includes seven subtests, including:

1. Visual discrimination
2. Visual memory
3. Visual-spatial relationships
4. Visual form constancy
5. Visual sequential memory
6. Visual figure ground
7. Visual closure

The test is independent of the motor and linguistic abilities of the person, and is not affected by culture race, gender, or level of education. Each subtest includes 16 pages, each consisting of 4-5 visual options. In each case, an image is presented to the child, whereby the child should choose the correct option. The test duration is not specific, though it usually takes 25 minutes to complete.

The number of correct responses of the child in each subtest is calculated and considered as the raw score of that subtest.

The test designer obtains each subtest after determining the raw score based on the child's age and using the standard tables presented. Then, based on the sum of the scaled scores of the seven areas mentioned above for each person, the visual perceptual quotient of that child is determined.

### Procedure

After receiving the ethics code from Isfahan University of Medical Sciences, the parents of all patients with hyperinsulinism, 4-13 years of age, referring to the Endocrine Clinic of Isfahan (29 patients), were contacted. The purpose of

conducting the visual perception screening test was then clearly communicated to the participants. Out of those briefed, 20 individuals agreed to participate in the study.

The necessary information in this research was collected by investigating the medical files of children in order to understand previous referrals of patients to ophthalmologists to be tested for refractive errors of the eye, strabismus, and the like. Eventually, the TVPS-3 test was performed on both the patient and healthy control groups to determine each subtest's visual perceptual quotient and scaled scores.

Specifically, each child was seated, whereby the pages of the TVPS-3 test were placed flat on a table in a small, quiet room, and the time required for each participant to complete the TVPS-3 depended on whether he or she reached the ceiling for every subtest. Furthermore, in the patient group, the frequency of convulsions and MRI changes, as well as developmental delays, language delays, strabismus, and age of diagnosis of hyperinsulinism were extracted from the data recorded in the medical file of patients and their history.

### Data analysis

For the analysis and mean comparison of the scaled score of each subtest and the total visual perceptual quotient between case and control groups, a t-test was employed. Cohen's d was also applied in order to estimate the effect size between the two groups. In this regard:

d= 0.2 (Small effect Size)

d= 0.5 (Moderate effect Size)

d= 0.8 (Large effect Size)

## Results

Overall, 40 children (20 patients and 20 healthy controls) were assessed in this study. The age of all children was 4-13 years and 12 months. There were 13 boys and seven girls in the patient group, while 12 boys and eight girls in the control group. The mean age in both groups was seven years.

Table 1 compares the mean visual perceptual quotient and the mean scaled score of the seven visual perception skills on TVPS-3 in 4-13-year-old children suffering from hyperinsulinism and the healthy control group. As inferred from the table, there is a significant difference between the healthy and patient groups in all areas of visual perception ($p\text{-value}<0.001$) . Correspondingly, a significant difference was observed between the two groups regarding the total visual perceptual quotient. By calculating the effect size of Cohen d, the real difference between the two groups (independent of the sample size effect) was also demonstrated, as the effect size in all variables has been greater than 0.8 due to the real difference between the two groups.

Children with hyperinsulinism exhibited significant deficits in three specific areas of visual perception compared to the control group. These areas include visual-spatial memory, visual closure, and visual-spatial relationships. In contrast, the remaining four areas of visual perception assessed showed that the case group's average scores were lower than those of the control group. The age of patients at the time of diagnosis of hyperinsulinism in this study ranged from one day to six months, with the mean age of diagnosis being 72.67 days. However, no significant relationship was found in this study between the age of disease diagnosis and the scaled

**Table 1**: Means, standard deviations (in brackets), and effect size for the different **subtests'** scaled scores and the perceptual quotients of the TVPS-3 test for each group

| Variables | Group | | | |
|---|---|---|---|---|
| | Control( n=17) | Case (n=29) | P-value | Cohen's d |
| Age (years) | | | - | - |
| Mean ± SD | 7.80± 2.33 | 7.84± 2.19 | | |
| Median [min,max] | 7[5,12] | 7[4,12] | | |
| Age diagnosis (day) | | | | |
| Mean ± SD | - | 72.67± 76.7 | - | - |
| Median [min,max] | - | 52.5[1,225] | | |
| Visual discrimination | | | 0.001* | 1.45 |
| Mean ± SD | 13.10± 1.52 | 7.60±5.14 | | |
| Median [min,max] | 13[11,17] | 8[1,18] | | |
| Visual memory | | | 0.001* | 1.25 |
| Mean ± SD | 12.20± 1.51 | 7.30±5.31 | | |
| Median [min,max] | 13[10,14] | 7.5[1,18] | | |
| Visual-spatial relationships | | | 0.001* | 1.85 |
| Mean ± SD | 12.50± 1.47 | 5.55±5.08 | | |
| Median [min,max] | 12.5[9,15] | 4.50[1,17] | | |
| Visual-form constancy | | | 0.001* | 1.55 |
| Mean ± SD | 12.55± 1.98 | 6.60±5.03 | | |
| Median [min,max] | 13[9,15] | 5.50[1,16] | | |
| Visual-sequential memory | | | 0.001* | 1.63 |
| Mean ± SD | 10.30± 2.77 | 5.85±4.70 | | |
| Median [min,max] | 9[8,18] | 5[1,19] | | |
| Visual-figure-ground | | | 0.001* | 1.43 |
| Mean ± SD | 12.95± 1.73 | 7.20±5.41 | | |
| Median [min,max] | 13[9,15] | 6.5[1,19] | | |
| Visual closure | | | 0.001* | 1.90 |
| Mean ± SD | 12.40± 1.73 | 5.55±4.65 | | |
| Median [min,max] | 12[10,17] | 4.5[1,17] | | |
| Perceptual quotient | | | 0.001* | 1.83 |
| Mean ± SD | 116.50± 7.56 | 80.50±26.74 | | |
| Median [min,max] | 115[108,134] | 72.5[55,145] | | |

**Table 2**: associated disorder

| | | Frq (Per.) |
|---|---|---|
| Seizure | Yes | 19(95.0) |
| | No | 1(5.0) |
| Speech delay | Yes | 7(35.0) |
| | No | 13(65.0) |
| Motor delay | Yes | 7(35.0) |
| | No | 13(65.0) |
| Strabismus | Yes | 1(5.0) |
| | No | 19(95.0) |
| MRI_ Change | No MRI | 7(35.0) |
| | Change | 6(30.0) |
| | No Change | 7(35.0) |

score in the seven subtests from TVPS-3 or the total visual perceptual quotient.

Based on Table 2, out of 4-13-year-old children with hyperinsulinism, 19 (95%) had convulsions and seven (35%) had language and motor delays. Among these children, strabismus was reported only in one child (5%), and six (30%) of them had MRI changes.

In this study, the mean visual perception among the 4-13-year-old children with hyperinsulinism and suffering motor delay, speech delay or strabismus was lower than children without these conditions. For example, the mean visual perceptual quotient in 4-13-year-old children suffering from hyperinsulinism with motor delay was 55.43, while those suffering from hyperinsulinism without motor delay was 94. On average, children with speech delays had a visual perceptual quotient of 66.71, compared to 87.92 in children without speech delays. Similarly, children with strabismus had an average visual perceptual quotient of 55, while those without the condition scored higher, averaging 81.84.

## Discussion

In this study, it was found that 4-13-year-old children with hyperinsulinism were weaker than healthy children in all areas of visual perceptual skills, including:

1. Visual discrimination
2. Visual memory
3. Visual-spatial relationships
4. Visual form constancy
5. Visual sequential memory
6. Visual figure ground
7. Visual closure,

as well as visual perceptual quotient.

In this study, again in children suffering hyperinsulinism, the mean visual perception of children who had changes associated with hypoglycemia in brain MRI was lower than that of children with reportedly healthy MRI.

Karimzadeh et al. also showed that neonatal hypoglycemia could be associated with hypoglycemia-occipital syndrome, including visual disturbances, as well as epilepsy and psychomotor retardation (17) ictal vomiting was more common in controls. Subjects were in epileptic and nonepileptic groups. Ninety percent of cases showed abnormal signal of the posterior head region on magnetic resonance imaging (MRI.

In the present study, the mean visual perception was lower in children suffering from hyperinsulinism with motor and speech delays than in children without these conditions. Seemingly, motor and speech delay is associated with impaired visual perception.

In this study, one out of the 20 patients suffering from hyperinsulinism had strabismus (5%) ; in this person, visual perception was lower on average

compared to children without this problem.

In a review article by Paudel et al. (6) it was stated that there can be a possible relationship between neonatal hypoglycemia and the presence of strabismus.

In this study, the mean age of diagnosis of hyperinsulinism was 72 d (from one day to six months of age) . However, no relationship was found between younger age at the time of diagnosis and the extent of damage to the visual perception. This can be due to a delayed diagnosis of hyperinsulinism.

Moreover, this study showed that in patients suffering from hyperinsulinism, three areas of visual-spatial relationships, visual sequential memory, and visual closure are impaired more than other areas of visual perception.

## Limitations and recommendations

One of the limitations of this study was that occupational therapy and visual perception interventions were not performed. Proposedly, future studies by performing occupational therapy investigate the extent of its impact on improving the visual perception of children suffering from hyperinsulinism.

## In Conclusion

Overall, this research showed that 4-13-year-old children suffering from hyperinsulinism can be screened via the TVPS-3 test in terms of visual perceptual disorders. Screening these children and diagnosing cases with visual perception problems may help initiate different rehabilitation programs among these patients.

## Acknowledgement

The authors are thankful from all the participants and their families. The Research and Ethics council of Isfahan University of Medical Sciences approved the study (Project number: 398393)

## Author's Contribution

Azin Momeni contributed to the conception and design of the work, data acquisition, analysis, interpretation, drafting and revising the article critically for important intellectual content. Mohammad Reza Ghazavi and Jafar Nasiri contributed to the concept and design of the study, and edited the final version of the manuscript. Mahin Hashemipour contributed to the data acquisition. All authors reviewed and approved the final version for submission. All authors accept the responsibility of the manuscript content.

## Conflict of interest

None declared

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