Assessment of Insulin-Like Growth Factor-1 Level in Neonates with Hyperbilirubinemia

Abeer Fathy, PhD¹, Rawia A. Swelam, PhD², Dalia A. Shaheen, PhD³

¹Department of Pediatrics, Mansoura University, Mansoura, Egypt
²Department of Pediatrics, Al Azhar University, Cairo, Egypt
³Department of Medical Biochemistry, Mansoura University

Address correspondence:
Abeer Fathy, PhD
Department of Pediatrics, Mansoura University
Mansoura, Egypt
E-mail: abeerfathy2000@yahoo.com

Author Disclosure: The authors have nothing to disclose.

ABSTRACT

Background: Kernicterus, or bilirubin encephalopathy, is a condition caused by bilirubin toxicity to the basal ganglia and various brainstem nuclei. Neither the cellular nor molecular mechanisms underlying bilirubin neurotoxicity are well understood. Insulin-like growth factor-1 (IGF-1) is a polypeptide hormone that has demonstrated effects on neural cells. The aim of this study is to find out the potential role of serum IGF-1 in neonatal hyperbilirubinemia.

Methods: Serum levels of IGF-1 were measured using ELISA in 40 term neonates with hyperbilirubinemia and 21 normal term neonates.

Results: Serum IGF-1 level in the hyperbilirubinemia group (50.95±12.26ng/L) was significantly lower than that in the control group (74.81±14.17 ng/L) (P<0.05). Serum IGF-1 levels were negatively correlated to the bilirubin level (r=-0.978, P: 0.000) in the hyperbilirubinemic group.

Conclusions: Serum IGF-1 levels decreased in neonates with hyperbilirubinemia and this reduction correlated with the degree of hyperbilirubinemia. IGF-1 might have a protective effect against bilirubin-induced brain damage.

Key Words: hyperbilirubinemia, IGF-1, kernicterus, neonatal jaundice

INTRODUCTION

Kernicterus, or bilirubin encephalopathy has been described in the medical literature for over a century. It is caused by bilirubin toxicity to the basal ganglia and various brainstem nuclei; however, neither the cellular nor molecular mechanisms underlying bilirubin neurotoxicity are well understood.¹

Evidence from in vitro studies suggests that bilirubin impairs mitochondrial function and viability of astrocytes. Higher concentrations impair mitochondrial function and cellular proliferation in neurons, and it can induce apoptosis.² Bilirubin also interferes with intracellular calcium homeostasis through several mechanisms and it may sensitize the cell to other injuries, and may cause neuronal hyperexcitability via excitatory amino-acid neurotoxicity.³⁶ Different factors are important determinants of bilirubin toxicity.
such as the neuronal susceptibility, degree of
differentiation at the time of exposure, the
amount and duration of exposure to free
bilirubin, and blood brain barrier function.\textsuperscript{7}

Insulin-like growth factor-1 (IGF-1) is a
pleiotropic factor with a wide spectrum of
action in the central and peripheral nervous
system.\textsuperscript{8,9} It belongs to a superfamily of
structurally related proteins that includes
insulin, IGF-1, and IGF-2. The biological
functions of IGF-1 are mediated by specific
membrane receptors designated IGF-1
receptors. There are six IGF-binding
proteins (IGFBPs), which modulate
bioavailability and receptor targeting of the
IGFs.\textsuperscript{9,10} The insulin-like growth factor
(IGF) system is expressed in most tissues
and organs during embryogenesis and
throughout adult life. In particular, it is
abundantly expressed during development of
the nervous system, playing a key role in
this process. Recently, IGF-1 has gained
increasing attention for the treatment of
neurodegenerative disorders, such as
amyotrophic lateral sclerosis.\textsuperscript{11,12} IGF-1 has
been found to protect hippocampal neurons
against the toxicity of the Alzheimer’s
disease-associated amyloid b protein (Ab).\textsuperscript{13}
Moreover, a more general protective
potency of IGF-1 against oxidative stress
has been documented in many studies. In
one study, the neuroprotective action of
IGF-1 was tested in immortalized
hypothalamic cells exposed to reduced
 glutathione depleting agents, which cause
oxidative stress and cell death. They
demonstrated a protective role for IGF-1
against glutathione depleting agents-induced
damage suggesting an antioxidant action of
this growth factor in hypothalamic
neurons.\textsuperscript{14} Another study demonstrated that
IGF-1 promotes the survival of rat primary
cerebellar neurons and of immortalized
hypothalamic rat cells after challenge with
oxidative stress induced by hydrogen
peroxide.\textsuperscript{15}

To date, there are few reports about the
relation between serum IGF-1 and brain
damage in neonates with hyper-
bilirubinemia.

**METHODS**

Forty term sequential neonates with
hyperbilirubinemia were selected to
participate in this study. They were 25 males
(62.5%), and 15 females (37.5%) with their
ages ranging from 3–5 days. A group of 21
age and sex matched normal neonates with
bilirubin levels less than 5 mg/dL (as
initially detected by bilirubinometry then
confirmed by laboratory assessment) were
taken as a control group. Informed consent
was obtained from at least one parent of
each neonate. The protocol of the study was
approved by the local ethical authority prior
to starting of the study.

**A-Clinical assessment:**

All neonates enrolled in the study were
subjected to complete physical examination
including anthropometric measures and
neurologic examination. All selected
neonates were full term with no evidence of
birth asphyxia, infection, congenital
anomalies or systemic diseases.

**B-Laboratory investigations:**

Three milliliters of venous blood was
collected from each subject and divided into
two samples. The first one was used for
blood chemistry analysis (total and direct
serum bilirubin and serum albumin) and
analyzed immediately. The other blood
sample was used for immunoassay of serum
human IGF-1 levels and the sera were stored
at –20 °C until thawed for the assays.
Total serum bilirubin (TSB), direct serum bilirubin (DSB), and serum albumin (ALB) levels were measured by the automatic biochemistry analyzer (Boehringer Mannheim, Germany).

Serum human levels of IGF-1 were measured using enzyme linked immunosorbent assay (ELISA) method (DRG International Inc., USA). The readings were measured on an ELISA reader (HumaReader HS) at 450 nm. The results were calculated by plotting the optical density for the standards versus the concentration of the standards on log/log paper, and the IGF-1 concentration was recorded.

Statistical analysis

Data were expressed as mean ± SD (standard deviation), minimum- maximum, and/or percentage as appropriate using SPSS (statistical Package for Social Science) software for Windows version 10. Statistical analyses were performed using nonparametric methods (unpaired, two-tailed Student’s t-test). The criterion of significance was a value of P < 0.05. Correlation studies were determined by Spearman rank order correlations.

RESULTS

Table 1 shows the clinical data and the laboratory parameters of both groups expressed as mean ±SD, minimum and maximum values. No statistically significant difference existed between control and hyperbilirubinemia groups regarding weight, length, head circumference, and albumin level. IGF-1 level was significantly lower in the hyperbilirubinemia group than in the control group (P < 0.05).

Table 2 shows correlation between IGF-1 level and total serum bilirubin, weight, length, and head circumference in the hyperbilirubinemia group. IGF-1 had significantly negative correlation with TSB (r: - 0.978, P: 0.000). There is no significant correlation between IGF-1 and weight, length, and head circumference in hyperbilirubinemic neonates.

DISCUSSION

Although the neuropathologic features of bilirubin–induced brain injury have been well known for decades, understanding of the mechanisms of neuronal damage and cell
death remains limited. Recently, IGF-1 has gained increasing attention as a neuroprotective agent. We detected a reduction in the IGF-1 level in neonates with hyperbilirubinemia as compared to its level in the age matched control group. Such reduction was negatively correlated to the severity of the hyperbilirubinemia. The reduction in IGF-1 level was not correlated with body weight or height. In the study of Skalkidou et al. on healthy full term neonates, they observed that IGF-1, IGF-2, and IGF binding protein-3 were inversely associated with the presence of neonatal jaundice, after controlling for blood protein levels. However; they did not correlate the reduction of IGF-1 and the degree of hyperbilirubinemia in these neonates. In another study Lui et al, studied the relation between IGF-1 and hyperbilirubinemia, and they found that the reduction of IGF-1 correlates with the severity of the disease. Other investigators have tried to find out the relation between IGF-1 and brain injury in hypoxic ischemic encephalopathy (HIE) in neonates. A reduction in the serum IGF-1 levels in neonates with HIE has been detected at both acute and convalescence stages of the disease. The reduction of IGF-1 level was correlated to the severity of HIE. In one study, they assumed that IGF-1 can be used as a marker for estimating the severity and outcome of neonatal HIE. Furthermore, many workers studied the neuroprotective role of IGF-1 in experimental models of ischemic brain injury. These data suggest a potential role for insulin-like growth factor-1 in preventing cerebral palsy due to perinatal asphyxia.

The molecular signaling pathways by which IGF-1 promotes survival of neurons have been partially characterized. IGFBP-modulated interaction of the IGF ligands with the IGF-1 receptor activates two major intracellular signaling pathways, namely, the mitogen-activated protein kinase or the phosphoinositol-3 kinase pathway. In vitro studies have demonstrated that the IGF ligands, via the above pathways, promote differentiation and proliferation and sustain survival, preventing apoptosis of neuronal and brain-derived cells. Furthermore, the IGF system appears to be involved in the regulation of many brain metabolic functions, including uptake and utilization of glucose, the major fuel of the nervous system.

Our findings, supported by previous studies, provide new emphasis on the association between IGF-1 paucity and kernicterus. Although these data cannot confirm a causative relation between reduced IGF-1 levels and bilirubin encephalopathy, they provide a testable hypothesis in which IGF-1 paucity either contributes to or permits bilirubin-induced neuron injury. If this hypothesis proves true, IGF-1 might be a beneficial therapy in infants with extreme hyperbilirubinemia.

REFERENCES

3. Conlee JW, Shapiro SM, Churn SB. Expression of the alpha and beta subunits of Ca2+/calmodulin kinase II in the
IGF-1 and Hyperbilirubinemia

Fathy et al.


