THYROID HORMONES CHANGES IN INFANTS AND CHILDREN WITH CEREBRAL PALSY

Thesis

Submitted For Partial Fulfillment of Master Degree In Pediatrics

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2009

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Dedication

To

My Dear Father

My Dear Mother

And to

My Uncle

Acknowledgement

*First of all, my thanks are to "**ALLAH**" the kind and the merciful, who gave me the power to perform and complete this work.*

*It is a great honor to express my deepest gratitude and appreciation to Prof. **Dr. May Fouad Nassar**, Assistant Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her brotherhood guidance, patientce, supervision, helpful criticism and instructions during the progress of this work giving me much of her time, effort and knowledge.*

*I wish also to express my great appreciation to **Dr. Maha Mohamed Awadallah**, Lecturer of Pediatrics, Faculty of Medicine, Ain Shams University, for her sincere guidance, kind supervision and great help.*

*I would like to express my deepest thanks for **Dr. Eman Saleh El-Hadidy**, Lecturer of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her valuable advice and suggestions.*

*I would like to express my deepest thanks for **Dr. Salwa Reda El-Batrawy**, Assistant Professor of Anthropology, National Research Center, for her valuable advice and suggestions.*

*My thanks are also to **all staff members and personnel of the Departments of Pediatrics and Clinical Pathology**, Faculty of medicine, Ain Shams University, and also to all persons and patients who helped me in completing this work.*

Ahmed Esmat

List of Abbreviations

ALT	: Alaine transaminase
AST	: Aspartate transaminase
BTX	: Botulinum-A toxin
BUN	: Blood urea nitrogen
CNS	: Central nervous system
CP	: Cerebral palsy
CT	: Computerized tomography
EEG	: Electro-Encephalography
EMG	: Electromyography
FRS	: Functional respiratory system
FT3	: Free triiodothyronine
FT4	: Free tetra-iodothyronine
GABA	: Gama aminobutyric acid
GMF	: Gross motor function
GTC	: Generalized tonic clonic convulsion
IM	: Intramuscular
IQR	: Inter quartile ranges
Mo	: Month
MR	: Mentral retardation
MRI	: Magnetic resonance imaging
N	: Number
PAX8	: Paired-box gene 8
PVL	: Periventricular leukomalacia
rpm	: Revolution per minute
rT3	: Reverse triiodothyronine
SBP	: Systolic blood pressure
SD	: Standard deviation
T3	: Triiodothyronine
T4	: Tetra-iodothyronine
TBG	: Thyroxine-binding globulin
TH	: Thyroid hormone
TR	: Thyrotropin
TRH	: Thyrotropin-releasing hormone
TSH	: Thyroid stimulating hormone
TTF-1	: Thyroid transcription factor-1
TTF-2	: Thyroid transcription factor-2
VLBW	: Very low birth weight

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INTRODUCTION

Cerebral palsy is a non-progressive disorder of posture or movement caused by a lesion of the developing brain ***(Ashwal et al., 2004)***.

The prevalence of moderately severe cases is approximately 2:1000 live births ***(Strauss et al., 1998)***.

Perinatal asphyxia is a known cause of cerebral palsy but accounts for only a few cases. Prenatal factors are a more important cause but are difficult to identify with precision in an individual patient ***(Fenichel, 2005)***.

Thyroid hormones are essential for normal behavioural, intellectual, and neurological development. Congenital hypothyroidism, if not treated, can result irreversible mental retardation, whereas thyroid diseases with more moderate impairment of thyroid function, such as resistance to thyroid hormone, cause less severe intellectual and behavioral abnormalities, including attention deficit and hyperactivity disorder ***(Hauser et al., 1998)***.

There has been only few studies conducted to find the changes of the thyroid hormones status in children with cerebral palsy and neurological pathology ***(Vasil'eva et al., 2005)***.

Aim of the Work

To study thyroid hormones profile (T_3 – T_4 – TSH) in children with cerebral palsy in order to diagnose thyroid hormone changes in those children, thereby offering treatment thus decreasing morbidity and improving neurodevelopmental outcome.

CEREBRAL PALSY

Definition:

Cerebral palsy (CP) is a diagnostic term used to describe a group of motor syndromes resulting from disorders of early brain development. CP is caused by a group of developmental, genetic, metabolic, ischemic, infectious and other acquired etiologies that produce a common group of neurologic phenotypes. Although, it has been considered a static encephalopathy, this term is not entirely accurate, because of the recognition that the neurologic features of CP often change or progress over time ***(Johnston, 2008)***.

Epidemiology:

The incidence of CP has varied in different series according to criteria of selection, time and community studied. A figure of between 1 and 3 cases per 1,000 live births has been quoted ***(Neltina, 2001 and Reddihough & Collins, 2003)***.

Studied prevalence of CP in two north east Italian provinces "Padua" and "Rovigo". The prevalence of CP markedly increased from 1960 to the mid-1980 and then decreased in 5 years period, 1985-1989. The prevalence of CP increased over the years of types related to preterm birth as diplegia while decreased with types associated with term babies such as dyskinesia. The variation in the prevalence of CP over

the years, with two peaks corresponding with the introduction of neonatal intensive care units in "Pauda" and "Rovigo", suggest that changes in neonatal care could influence the levels of CP independent of the original presence of predisposing prenatal factors ***(Michele et al., 1999)***.

Disserved significant increase in CP prevalence rates, more specifically in CP not associated with severe mental retardation. This increase was only significant among children registered before the age of 6 years and may be related to an increase of early registeration ***(Rumeau et al., 1997)***.

Risk Factors:

A multiple of risk factors both environmental and genetic has been associated with the development of CP. These factors are prenatal, natal or postnatal.

1. Prenatal Risk Factors:

Prenatal risk factors include hyperemesis gravidarum, pregnancy included hypertension, threatened abortion, placentaprevia, abruptioplacenta, intrauterine bacterial and viral infections, chromosomal abnormalities, maternal malnutrition, and family history of CP ***(Deborah, 1997)***.

2. Natal Risk Factors:

Natal risk factors include breech delivery, multiple gestation, asphyxia, low Apgar score, periventricular leucomalacia, especially prematurity and low birth weight ***(Deborah, 1997)***.

3. Postnatal Risk Factors:

Postnatal risk factors include head trauma, seizures, hyperbilirubinemia, intracranial infections, toxic encepholo-pathies, cerebral and intraventricular haemorrhage ***(Deborah, 1997)***.

Other risk factors associated with an increased risk of CP include patent ductus arteriosus, hypotension, blood transfusion, prolonged ventilation, pneumothorax, sepsis, hyponatremia and total parenteral nutrition. Seizures were associated with an increased risk of CP as were parenchymal damage and an appreciable ventricular dilatation ***(Stelmach et al., 2005)***.

The rate of CP among very low birth weight infants (VLBW<1500g) may be from 60 to 70 times higher than the rate among normal birth weight infant. Although very low birth weight infants represent only about 1% of all births, their high risks for developmental impairment in combination with substantial improvement in the survival of VLBW infants have

lead to the observation that, among children born since about the mid 1970s, there are proportionately more individuals with CP (28%) or mental retardation (MR) (4-11%), who were of VLBW ***(Schendel et al., 1996)***.

Accardo et al. (2004) studied the incidence of cranial ultrasonographic lesions and CP in VLBW infants; they concluded that improved survival in VLBW infants since 1990 has been accompanied by a fall in parenchymal cerebral hemorrhages and subsequent CP rates in survivors.

Arpino et al. (1999) studied 51 children with combined CP, MR and epilepsy, 31 children with both CP and MR and 48 children with CP alone. They found that the patients with a combined diagnosis of CP, MR and epilepsy differ from patients with CP, either alone or with mental retardation the most striking difference was found to be a history of neonatal convulsions and a family history of epilepsy in the first degree relatives.

Judith et al. (1999) studied the association of neonatal interferons with spastic CP. In this study of predominantly term infants 14 of 31 children with spastic CP had concentrations of interferons, and in neonatal blood that exceed levels for the neonatal comparison group and also exceeded normal adult levels. Most of the children with spastic diplegic form of CP were among those with high concentration of interferons.

Pathology:

The primary problem in children with CP is lack of motor control that is caused by a central (brain) injury. This injury alters the integrative ability of the CNS in relation to motor function. The type of abnormality in movement and tone is related to the area of the brain that has been damaged. Meanwhile, damage to the cortex produces spasticity and basal ganglia damage results in athetoid movement, whereas cerebellar insults are associated with ataxia ***(Piper, 1998)***.

Pathophysiology showed that CP caused by the permanent neurologic lesions that range from gross brain malformations to vascular occlusion, neuron loss and laminar degeneration ***(Rollant et al., 2001)***.

Furthermore, the site of lesion and the type of disability varies with the gestational age. In preterm infants, the injury usually involves the white matter and the motor fibers of the lower extremities; thus injured preterm infants generally have a spastic diplegia, primarily of the legs, with normal or near-normal cognitive development because the gray matter of the cortex is not injured. This injury in term infants, usually from a hypoxic ischemic insult such as perinatal asphyxia, usually results in a parasagittal cortical lesions and leads to involvement of the upper extremities, face and tongue with impairment of speech ***(Stelmach et al., 2005)***.