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Newborn thyroxine levels and childhood ADHD

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Abstract

Objectives—Normal brain development is highly dependent on adequate levels of iodine and thyroid hormone. It has been suggested that Attention Deficit Hyperactivity Disorder (ADHD) is the consequence of prenatal thyroidal endocrine disruption. The hypothesis was examined using neonatal thyroxine levels as a bio-marker of prenatal thyroid status and comparing it to subsequent development of ADHD.

Design and methods—In a matched case-control study, cases were defined as children diagnosed with ADHD, while children born in the same hospital and tested on the same day served as matched controls. Conditional logistic regression analysis with unequal numbers of controls was performed.

Results—The neonatal thyroxine levels were within normal limits for each of the children who were subsequently diagnosed as having ADHD, and their distribution was no different from that of their controls.

Conclusions—Children diagnosed with ADHD do not demonstrate prenatal thyroidal dysfunction as reflected in the newborn thyroxine levels, therefore neonatal thyroxine levels are not a bio-marker for the subsequent development of ADHD.

Keywords

Neonatal thyroxine (T₄); Thyroid hormone; Attention deficit hyperactivity disorder; ADHD; Thyroid dysfunction

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a psychiatric diagnosis based on behavioral criteria as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). ADHD is a neurobehavioral disorder that usually appears in early childhood and generally before the age of 7. The prevalence of ADHD vary depending on

the population sampled, and is estimated to affect 4 to 12% of school-aged children in the U.S., thus making it the most common behavioral disorder in children [1].

Abnormal thyroid function can have a range of behavioral effects, ranging from severe neuropsychological deficits in children with congenital hypothyroidism [2], hyperactivity associated with hyperthyroidism, and impaired concentration arising from hypothyroidism. The etiology of primary ADHD is yet unknown. One hypothesis is that intrauterine thyroidal dysfunction during the period of prenatal neurologic structural development may be a causal factor for ADHD.

The hypothesis that neurodevelopmental abnormalities might be related to the thyroid is plausible. It is well known that both severe iodine deficiency [3] and untreated congenital hypothyroidism [4] result in mental retardation (cretinism). Newborn infants with congenital hypothyroidism who are identified by screening programs and treated promptly, at five to seven years of age usually display normal neurodevelopment, have IQs in the normal range, as well as normal growth. Even children born without a thyroid have normal intellect if thyroid hormone treatment starts early [5].

The thyroid system of the fetus develops independently of the mother's, however, the fetus is dependent on the maternal-placental system for adequate iodine supply throughout its development [6]. Maternal thyroxine (T_4) is generally sufficient to supply enough thyroid hormone to the fetus to take care of the developing fetal brain, although the fetal thyroid hormone levels are lower than normal. In the absence of a functioning fetal thyroid, the maternal thyroid hormone crossing the placenta is usually able to sustain a fetal thyroxine blood level of 40 to 60 nmol/L [7,8]. Children's IQs are generally normal if the newborn's T_4 level is 43 nmol/L or higher [9] and if the postnatal treatment is sufficient to restore the serum thyroid stimulating hormone (TSH) to normal levels (about 6–11 $\mu\text{g/kg/day}$ thyroxine) [10]. Newborns with congenital hypothyroidism treated with thyroxine within two weeks of birth show no intellectual deficit [11]. Fetuses with a normal fetal thyroid whose mothers are taking appropriate doses of antithyroid medications also have normal levels of thyroid hormones [12]. Studies of children born to mothers who were treated with antithyroid drugs during pregnancy have normal IQs (not different from comparison children) [13,14,15,16], although there is some suggestion of an effect on attention disorder [17]. These data suggest that women treated for hyperthyroidism during pregnancy are generally euthyroid. Undetected or inadequately treated maternal hypothyroidism in the second trimester has been associated with decreased IQ scores in the offspring in the absence of neonatal hypothyroidism [18].

Thyroid hormone is critical for brain development [19, 20,21,22]. The fetus depends solely on maternal thyroid hormones during the first trimester of pregnancy [23]. In the second and third trimester of fetal and brain development, thyroid hormone comes from both the maternal and fetal thyroid glands. An impact on neuropsychomotor development has been associated with subclinical maternal thyroid dysfunction in the first trimester, based on the presence of antibodies against the enzyme thyroid peroxidase [24] and on low but normal free T_4 levels [18,25], but not on low triiodothyronine (T_3) or high TSH levels. A decrease in the IQ of children, and a suggestion of an association with ADHD has been observed from cases of undiagnosed or under-treated second trimester maternal hypothyroidism, as determined by higher maternal TSH measurements. [18] No study has been done to determine whether ADHD is associated with intrauterine thyroid dysfunction assessed by neonatal thyroid function tests.

Since early treatment of congenital hypothyroidism is critical in preventing neurobehavioral disorders and neurodevelopmental consequences, the thyroid status of all newborn in the

United States is routinely assessed through congenital hypothyroidism screening programs using neonatal T₄ and or TSH levels after birth. To test the hypothesis that intrauterine thyroid dysfunction may be an early factor in the development of ADHD, we conducted a case-control study of children diagnosed at academic pediatric centers as having ADHD by identifying their neonatal T₄ levels and comparing them with matched neonatal controls.

2. Methods

2.1. Study design

This is a matched case/control study designed to determine whether children subsequently diagnosed with ADHD had abnormal neonatal thyroid hormone levels. ADHD cases diagnosed at the pediatric neurodevelopmental diagnostic clinics of the three medical schools in Washington D.C. served as potential cases. The data from the D.C. neonatal screening program were reviewed to identify the potential cases that had been born in Washington, D.C. and to record their neonatal T₄ values. The controls were new-borns screened on the same day as the case and born at the same hospital. The neonatal T₄ values of the controls were identified and compared with those of the cases.

The pediatric neurodevelopmental diagnostic clinics of the three medical schools in Washington D.C. were recruited for participation in this study. The institutional review board of each medical school approved the protocol, as did the director of the D.C. Health Department. Each clinic prepared a list of children diagnosed there as having ADHD along with their date of birth. These lists were submitted to the Neonatal Screening Laboratory at Howard University Hospital that had conducted the screening for the Division of Maternal and Child Health, D.C. Department of Health, Washington, D.C. Laboratory records were searched to identify the screening results for each case. Neonatal T₄ level measurements were retained in this laboratory as numeric date with actual values, as contrasted to laboratories elsewhere which retained only the categorical information of normal or abnormal.

Neonatal T₄ level as well as the date of sampling, date of birth, race, and sex of each case and all of its controls were recorded as a set with study numbers replacing personal identifiers. Cases or controls that were born premature were noted and excluded from the analysis. As all the children who met the matching criteria were retained as controls, the number of matched controls per case varied. The data from the three centers were pooled for analysis.

2.2. Subject recruitment and screening

Diagnostic clinics of the three medical schools in Washington D.C. (Howard University, George Washington University Childrens' National Medical Center, and George-town University) diagnosed the cases independent of this analysis. Assessments involved a full psychiatric interview with each child and each parent, and supplementary parental, teacher, and child interview materials and questionnaires. Children included in this study were diagnosed by an interdisciplinary team. Diagnostic teams consisted, at a minimum, of a psychologist and a developmental pediatrician, with additional team members, such as a physical therapist, occupational therapist, special educator, and speech and language specialist, based on the specific needs of each individual child. All children received a neuropsychological assessment designed to be age-appropriate and to address the presenting symptoms of the child.

This study was designed to maintain confidentiality with the specific diagnoses of individual cases maintained by the child's clinic. Informed consents were not required as this study was

limited to the analysis of currently existing data-sets and did not involve patient contact or follow-up.

2.3. Diagnostic and assessment instruments

Diagnosis of ADHD was performed according to usual clinical standards. All case children met the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria. While the test procedures varied among institutions, the domains measured consistently included abstract and concept formation, complex problem solving, cognitive speed, verbal learning, memory—both distant and short term, attention and alertness, visuo-spatial relationships, sensory function, and motor function. Typically, an intelligence measure such as one of the Wechsler Scales and an achievement measure such as the Woodcock Johnson Test of Achievement revised were used. These were supplemented by a variety of other procedures, tools, and tests to address the various domains in question. Age and presenting questions influenced the choice of evaluation tools in most instances.

2.4. Newborn thyroxine laboratory measurements

Collection of samples—Blood specimens were obtained, by the heel-stick method, within 48 to 72 h of birth. The blood specimens were collected at the nursery on a special S & S #903 filter paper. The specimens were allowed to dry at room temperature before transport of the dry blood specimen (DBS) to the laboratory.

Thyroxine (T_4) assays were performed on a $\frac{1}{8}$ " disc of the DBS by using ICN Neonatal (^{125}I) T_4 Solid Phase Radioimmunoassay System. [26] The TSH assays were performed on a $\frac{1}{4}$ " disc of the DBS using ICN Immuno-Chem™ Neonatal hTSH IRMA kit [27]. The same procedure and equipment were used to measure the samples of all of the cases and all of the controls.

2.5. Reference ranges

The reference ranges for T_4 were: 7 to 25 $\mu g/dL$ (90–276 nmol/L) are the normal limits, and values lower than 7 $\mu g/dL$ (90 nmol/L) are considered abnormal. The reference ranges quoted were supplied by the kit manufacturers and were used throughout the study. The abnormal specimens are then assayed for TSH. The reference ranges for TSH 0–30 $\mu IU/mL$ are the normal limits, and TSH values above 40 $\mu IU/mL$ are suggestive of hypothyroidism. The reference values for T_4 and TSH were derived from six controls: three controls from the specific manufacturer of these kits and three controls from the Center for Disease Control (CDC). Additionally, five controls from CDC were assayed quarterly for the proficiency testing. All the participating laboratories performing the neonatal newborn screening internationally and in the USA assay these CDC proficiency-testing samples.

2.6. Statistical analysis

To explore the relationship between neonatal blood thyroxine levels (T_4) and subsequent diagnosis of ADHD, a matched case-control design was employed. To improve generalizability, multiple sets of matched controls were defined to compare with cases in terms of neonatal blood thyroid hormone levels. Matched controls were created as follows: (1) Controls matched on age, sex and race; (2) Controls matched on age and sex; (3) Controls matched on age and race; and (4) Controls matched on sex and race.

Conditional logistic regression analysis with unequal numbers of controls was performed since this is a matched case-control study with unequal numbers of controls. [28] Conditional logistic regression analyses were performed separately for different sets of controls.

To examine the relationship between T_4 and disease status, T_4 was treated both as a categorical and as a continuous variable in the logistic regression analysis. Using T_4 as a categorical variable, we calculated quantiles (the first –25th percentile, the second –50th percentile or median, and the third –75th percentile) of T_4 . The values of T_4 above the third quantile were used as a reference group. Thus, three dummy variables were then created and were put into the logistic regression analysis. Statistical tests were considered to be significant at an alpha level of 0.05 on a two-tailed test.

3. Results

Fifty-two children diagnosed with ADHD at medical school diagnostic clinics in Washington, DC and who had been full-term births in Washington DC hospitals served as the case group. All cases were between 5½ and 12 yr of age at time of diagnosis. Births occurred between 1988 and 1996. Matched controls were those newborns whose neonatal screening occurred on the same day and in the same hospital as the case, with one to five matched controls per case. The neonatal serum T_4 level on each case and each control were obtained. Additional information on cases and controls included age at time of sampling, race, and sex. Analysis took these other variables into consideration.

All ADHD cases seen here were found to have had neonatal T_4 levels within the normal range for newborns, as did the controls (Figures 1 and 2).

1. **Analysis for ADHD case-control sets, matched on age, sex, and race.** Fifty two cases and 71 controls were included in the analysis, and the results of regression analysis (Table 1) indicate that the association between T_4 levels and disease status of ADHD was not significant when T_4 was coded as continuous or categorical and matched on age, sex, and race.
2. **Analysis for ADHD case-control sets, matched on age and sex.** Fifty-two cases and 118 controls were included in the analysis, and the results of regression analysis (Table 2) indicate that the association between T_4 levels and disease status of ADHD was not significant when T_4 was coded as continuous or categorical and matched on age and sex.
3. **Analysis for ADHD case-control sets, matched on age and race.** Fifty two cases and 130 controls were included in the analysis and the results of regression analysis (Table 3) indicate that the association between T_4 levels and disease status of ADHD was not significant when T_4 was coded as continuous or categorical and matched on age and race.
4. **Analysis for ADHD case-control sets, matched on sex and race.** Fifty two cases and 76 controls were included in the analysis and the results of regression analysis (Table 4) indicate that the association between T_4 levels and disease status of ADHD was not significant when T_4 was coded as continuous or categorical and matched on sex and race.

All analytic sets found no difference in the neonatal T_4 levels for ADHD cases as for their controls, whether T_4 was analyzed as a categorical or continuous variable.

4. Discussion

The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), describes three patterns of behavior that may indicate ADHD: consistent inattention, hyperactivity, and impulsive behavior, or combinations of these three behaviors [29]. The fundamental causes of ADHD are not known; however, most researchers agree that it is a brain disorder with a biologic basis [30,31]. Some genetic and environmental elements are believed to be

important contributors to the etiology of ADHD [32,33], although other environmental contaminants that are known goitrogens have not been associated with it [34]. The finding that up to 60% of patients with resistance to thyroid hormone (RTH) also have ADHD focused attention on thyroid dysfunction as a potential cause of ADHD [35]. However, subsequent research demonstrated that most of ADHD patients do not exhibit RTH. In addition, patients with ADHD usually have normal thyroid hormone levels [30,36].

It is well established that frank hyperthyroidism can cause psychiatric syndromes, including anxiety, depression and overactivity (hyperkinesia) [37,38]. It is also well established that RTH produces a variable clinical presentation despite having a relatively restricted genetic mutation in the thyroid beta receptor gene [39]. A leading hypothesis to explain the varying clinical presentations, is differing tissue expression of the α -form of the thyroid hormone receptor, which is not genetically lesioned, as well as expression of thyroid hormone receptor associated protein (TRAP) cofactors [39]. The heart, for example, primarily expresses the alpha receptor whereas the liver primarily expresses the beta receptor [40]. Thus, tachycardia, a sign of hyperthyroidism, can co-exist with signs of a “hypothyroid” liver, in the same patient [41]. Similarly, the brain (which also expresses primarily the alpha receptor) can theoretically display signs of ADHD resulting from the resistance to thyroid hormones.

Thyroid hormones play a critical role in brain development [21,42,20,22]. As noted by Glinioer *et al.* [43], the adequate functioning of both the maternal and fetal thyroid glands play an important role to ensure that the fetal neuropsychological development progresses normally. Lack of a fetal thyroid gland (congenital athyroidism), maternal thyroid dysfunction (hypothyroidism), antithyroid antibodies and iodine deficiency all can impact brain development. It is well known that extreme iodine deficiency [3] and untreated neonatal hypothyroidism severely impacts brain development, leading to mental retardation and psychomotor dysfunction. Lesser degrees of thyroid dysfunction do not cause frank mental retardation, but can result in more subtle but measurable neurocognitive and psychomotor deficits, as observed in children with early treated congenital hypothyroidism [4,44,45,46,47]. Consistent with these observations, pregnant women with subclinical hypothyroidism [18,48], women in geographical areas of mild iodine deficiency [49,50], women with normal but low free T₄ (hypothyroxemia) [51], and women with antithyroid per-oxidase antibodies [24] may give birth to children who subsequently demonstrate mild but measurable neurocognitive and psychomotor deficits in early childhood. In light of observations that intrauterine thyroid dysfunction can lead to disturbances of attention [52,53,54,55,56], the fact that premature birth, which is accompanied by transient hypothyroidism, increases the risk of developing ADHD [57], and the co-morbidity of ADHD with learning disabilities [31], we tested the hypothesis that neonatal T₄ could predict the subsequent development of ADHD. As demonstrated in the results, this is not the case.

ADHD is a major neurobehavioral disease of childhood. The ADHD cases in this study had normal neonatal T₄ levels that did not differ from the neonatal T₄ levels of their matched controls, demonstrating no relationship. Similar studies might be conducted assessing the neonatal screening data of children with other pediatric diseases.

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Fig. 1.
Cumulative distribution of neonatal T₄s for cases and controls.

Fig. 2.
Neonatal T₄ distribution (%) of cases and controls.

Table 1

Conditional logistic regression analysis of ADHD in relation to T4 levels case-control sets matched on age, sex and race.

T ₄ $\mu\text{g/dL}$	Odds ratio	95% CI	P-value
>16.7	1.00		
12.3	0.71	(0.20, 2.45)	0.59
12.4–14.4	0.95	(0.37, 2.44)	0.91
14.5–16.7	1.35	(0.49, 3.70)	0.56
Continuous	1.08	(0.95, 1.24)	0.26

Table 2

Conditional logistic regression analysis of ADHD in relation to T₄ levels case-control sets matched on age and sex

T ₄ μ g/dL	Odds ratio	95% CI	P-value
>16.7	1.00		
12.3	0.86	(0.29, 2.50)	0.78
12.4–14.4	1.12	(0.48, 2.62)	0.79
14.5–16.7	1.22	(0.50, 2.95)	0.66
Continuous	1.03	(0.92, 1.16)	0.61

Table 3

Conditional logistic regression analysis of ADHD in relation to T4 levels case-control sets matched on age and race.

T ₄ $\mu\text{g/dL}$	Odds ratio	95% CI	P-value
>16.7	1.00		
12.3	0.74	(0.25, 2.21)	0.58
12.4–14.4	0.95	(0.49, 2.54)	0.79
14.5–16.7	1.25	(0.50, 3.12)	0.63
Continuous	1.06	(0.95, 1.19)	0.29

Table 4

Conditional logistic regression analysis of ADHD in relation to T₄ levels case-control sets matched on sex and race.

T ₄ $\mu\text{g/dL}$	Odds ratio	95% CI	P-value
>16.7	1.00		
12.3	0.60	(0.18, 2.01)	0.41
12.4–14.4	0.83	(0.33, 2.11)	0.70
14.5–16.7	1.37	(0.50, 3.72)	0.54
Continuous	1.11	(0.98, 1.26)	0.10