Attention Deficit and Hyperactivity Disorders in the Offspring of Mothers Exposed to Mild-Moderate Iodine Deficiency: A Possible Novel Iodine Deficiency Disorder in Developed Countries

F. VERMIGLIO, V. P. LO PRESTI, M. MOLETI, M. SIDOTI, G. TORTORELLA, G. SCAFFIDI, M. G. CASTAGNA, F. MATTINA, M. A. VIOLI, A. CRISÀ, A. ARTEMISIA, AND F. TRIMARCHI

Dipartimento Clinico-Sperimentale di Medicina e Farmacologia-Sezione di Endocrinologia (F.V., V.P.L.P., M.M., G.S., M.G.C., F.M., M.A.V., F.T.), Dipartimento di Scienze Pediatriche-Sezione di Neuropsichiatria Infantile (M.S., G.T., A.C.), and Dipartimento di Diagnostica di Laboratorio-Servizio di Biochimica Clinica (A.A.), University of Messina, Messina 98125, Italy

Over a period of almost 10 yr, we carried out a prospective study of the neuropsychological development of the offspring of 16 women from a moderately iodine-deficient area (area A) and of 11 control women from a marginally iodine-sufficient area (area B) whose thyroid function had been monitored during early gestation.

Attention deficit and hyperactivity disorder (ADHD) was diagnosed in 11 of 16 area A children (68.7%) but in none from area B. Total intelligence quotient score was lower in area A than in area B children (92.1 ± 7.8 *vs.* 110 ± 10) and in ADHD children when compared with both non-ADHD children from the same area and control children (88.0 ± 6.9 *vs.* 99.0 ± 2.0 and 110 ± 10, respectively). Seven of 11 ADHD children (63.6%) were born to the seven of eight area A mothers who became hypothyroxinemic at early gestation, whereas only one of five non-ADHD children was born to a woman who was hypothyroxinemic at 20 wk of gestation.

So far, a similar prevalence of ADHD has been reported only in children with generalized resistance to thyroid hormones. This might suggest a common ADHD pathogenetic mechanism consisting either of reduced sensitivity of the nuclear receptors to thyroid hormone (generalized resistance to thyroid hormones) or reduced availability of intracellular T_3 for nuclear receptor binding. The latter would be the ultimate consequence of maternal hypothyroxinemia (due to iodine deficiency), resulting in a critical reduction of the source of the intracellular T_3 available to the developing fetal brain. (*J Clin Endocrinol Metab* 89: 6054–6060, 2004)

NONSYSTEMATIC OBSERVATIONS IN a moderately iodine deficiency (ID)-endemic goiter area in Northeastern Sicily, where we described children's defective neuromotor and cognitive ability (1) along with transient maternal thyroid failure during early (2) and late (3) gestation, revealed an unexpectedly high occurrence in schoolchildren of a developmental disorder whose symptoms, which included difficulties in sustaining attention and hyperactivity, were suggestive of attention deficit and hyperactivity disorder (ADHD). This syndrome has been reported to be strongly associated with generalized resistance to thyroid hormone (GRTH) (4).

The present long-term prospective study was carried out on the offspring of a series of women, all born and living in the same moderately ID area, whose thyroid function was studied during early pregnancy with the aim of identifying the long-term effects of ID-related maternal hypothyroxinemia on the behavioral, psychoneurological, and intellectual development of children.

Subjects and Methods

Participants

The study group included 16 children born to 16 healthy mothers living in the moderately ID and extensively studied area (area A) and 11 control children born to 11 age-matched women from an area with marginally sufficient iodine intake (area B).

Table 1 shows the characteristics of both areas when the children were conceived (1990–1992) and at the present time.

Neuropsychological and neurological assessment

To rule out other psychiatric or primary disorders that would more adequately explain the clinical picture of ADHD, we combined staff from the departments of endocrinology, neurology, developmental pediatrics, and psychology (5). The first behavioral and neuropsychological evaluation (1994) was performed on a clinical observation basis when the children were 18–36 months old by two independent examiners (M.S. and G.T.), who were unaware of their mothers' thyroid function during pregnancy. All children from both areas A and B were subsequently reevaluated (2001–2002), by the same examiners, when they were 8–10 yr old. Besides neurological examination and ADHD screening, the second evaluation included intelligence testing to rule out mental retardation, in which inattention and hyperactivity symptoms are commonly found.

Neurological evaluation, carried out according to the directions of Touwen (6) when the children were 18–36 months and 8–10 yr old, included assessment of the child while sitting, standing, walking, and lying, as well as examination of muscle tone, reflexes, and general data (dominance, fine motor coordination, sensory examination, speech, and language).

TABLE 1. Epidemiological characteristics of the two areas where the study was carried out

	1990–1992		2000	
	Area A	Area B	Area A	Area B
Urinary iodine excretion (μg/d)	48.1 ± 38.2	95.2 ± 55.8	63.0 ± 35.4	115.2 ± 61.4
% goiter in schoolchildren	24.7	7.8	16.3	3.5

Area A refers to the iodine-deficient area where the 16 pregnant women lived and bore their offspring. Area B is a sea-level small town where the 11 control mothers resided.

Screening for ADHD

The reference scale for inattention and hyperactivity derives from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition-Text Revision (DSM-IV-TR) (7), validated by subscales for the Italian population (8). The essential feature of ADHD is a persistent pattern of inattention and/or hyperactivity-impulsivity. Analysis of the structured psychiatric interviews makes it possible to identify different subtypes of the disorder, depending on the prevalence (and persistence for at least 6 months) of different symptoms (nine for the attention deficit variant and nine for the hyperactive variant): 1) ADHD, combined type subtype (6 of 9 or more inattention symptoms and six of nine or more hyperactivity/impulsivity symptoms); 2) ADHD, predominantly inattentive type subtype (six of nine or more inattention symptoms but fewer than six of nine hyperactivity/impulsivity symptoms); 3) ADHD, predominantly hyperactive-impulsive type subtype (six of nine or more hyperactivity-impulsivity symptoms but fewer than six of nine inattention symptoms). The minimum score for a child to be considered to be affected with ADHD was, therefore: six of nine for both ADHD predominantly inattentive type, and ADHD predominantly hyperactive-impulsive type subtypes; and at least 12 of 18 for the ADHD combined type subtype.

The questionnaires with the items listed in the DSM-IV-TR were distributed both to parents and to teachers when the children's ages ranged between 8 and 10 yr, with directions to mark each item "often", "sometimes", "rarely", or "never". An item was considered positive when both parents and teachers marked it "often".

Intelligence testing

Intelligence was measured by the most widely used intelligence test, the Wechsler Intelligence Scale for Children, 3rd edition (WISC-III) (9), which provides a full-scale intelligence quotient (IQ) score and subscale scores (range, 40–160) for verbal skills and performances in the following areas: general information, general comprehension, arithmetic, similarities, vocabulary, digit span, picture completion, picture arrangement, block design, object assembly, coding, and mazes.

The WISC-III full-scale IQ score comprises three subscores devoted to items considered free from distractibility (arithmetic, digit span, and coding—WISC-III freedom-from-distractibility score); to verbal items (general information and comprehension, arithmetic, similarities, vocabulary, and digit span—WISC-III verbal IQ score) and to performance items (picture completion and arrangement, block design, object assembly, coding, and mazes—WISC-III performance IQ score).

According to this scale, a child is considered to be mentally retarded when his total IQ (t-IQ) score is less than 75 points (10).

Children's thyroid function tests

All children were euthyroid at delivery, as proved by the results of neonatal screening for congenital hypothyroidism. Serum free T_3 (FT_3), free T_4 (FT_4), and TSH were measured in all children when they were 18–36 months old (January-June 1994) using the same commercial kits as used to study their mothers (see below) and at 8–10 yr (November 2001-May 2002) using commercial kits supplied by Diagnostic Products Corporation, Los Angeles, CA (Immulite 2000 Analyzer).

Maternal thyroid function tests

We measured serum T_3, T_4, FT_3, FT_4, TSH, and T_4-binding globulin (TBG) values at three different points in time (between 5 and 10, 11 and 14, and 18 and 20 wk of gestation). These correspond approximately to times before (8–13 wk) and subsequent to (20 wk) the onset of secretion

of thyroid hormones by the fetal thyroid and will be referred to as 8, 13, and 20 wk of pregnancy, respectively. TBG saturation by T_4 was calculated as the molar T_4/TBG ratio, assuming 57 kDa to be the molar mass for TBG.

Maternal circulating total T_4 and T_3 (RIA), TSH (immunoradiometric assay), FT_3 and FT_4 (Amerlex-MAB, a one-step radiolabeled analog RIA) were determined (1990–1994) using commercial kits supplied by Kodak Clinical Diagnostic Ltd., Amersham, UK. Precision profiles showed inter- and intraassay coefficients of variation not exceeding 5%, over the entire measurement range, for both free thyroid hormones.

Serum antithyroid antibodies were measured using a two-step immunoenzymometric assay supplied by Tosoh Corporation, Tokyo, Japan (AIA-PACK TgAb and TPOAb). TBG concentration was measured using a commercial RIA kit (Behring, Marburg, Germany).

Definition of hypothyroxinemia

The term hypothyroxinemic is used here and elsewhere to indicate pregnant women with normal TSH concentrations (0.4–4.0 μU/ml) but low serum FT_4 values as compared with the range values calculated (mean ± 2 SD) at the same stage of pregnancy (8, 13, and 20 wk) in a series of 50 healthy women with moderately adequate iodine intake (150–200 μg iodine/d). Accordingly, normal values at 8 wk were: 1.02–1.72 ng/dl; mean ± SD, 1.36 ± 0.17; median, 1.39 (13.1–22.2 pmol/liter; mean ± SD, 17.6 ± 2.25; median, 17.9). Normal values at 13 wk were: 0.98–1.49 ng/dl; mean ± SD, 1.24 ± 0.12; median, 1.25 (12.7–19.2 pmol/liter; mean ± SD, 16.0 ± 1.64; median, 16.2). At 20 wk, values were: 0.85–1.39 ng/dl; mean ± SD, 1.12 ± 0.13; median, 1.11 (11.0–17.9 pmol/liter; mean ± SD, 14.5 ± 1.7; median, 14.3).

Statistical analysis

Unless otherwise indicated, data are expressed as mean ± SD. Statistical analysis was performed by two-way ANOVA, linear regression, Student's t test for unpaired data, and the χ^2 test.

Informed written consent was obtained from all the mothers recruited and from both the children's parents.

Results

Endocrine and neuromotor evaluation in children

All the children from both areas were euthyroid at neonatal screening and afterward (18–36 months and 8–10 yr) (data not shown). At clinical neuromotor evaluation, no child showed any neurological signs typically belonging to the spectrum of ID disorders (11).

ADHD testing

In nine of 16 children from area A, clinical observation in 1994 had revealed the presence of psychoneurological features suggestive of ADHD. This diagnosis was confirmed in 2001–2002 (DSM-IV-TR) in all of them and in a further two area A children in whom ADHD had not been suspected in 1994. None of the 11 area B children were affected with ADHD, because the tentative diagnosis made in 1994 for one of them was not confirmed in 2001–2002.

Therefore, ADHD affected 11 of 16 (68.7%) children from area A (5 of 11 ADHD, combined type subtype; five of 11

ADHD, predominantly hyperactive-impulsive type subtype; and one of 11 ADHD, predominantly inattentive type subtype).

To improve the readability of the further results, the area A children and (their respective) mothers will henceforth be referred to as ADHD+ve and ADHD−ve area A subgroups, according to the presence or absence of ADHD, respectively.

Intelligence testing

Full-scale IQ score and subscale scores for each item are summarized in Table 2.

The WISC-III was completed for all children except one from area A, in whom extreme inattention and hyperactivity made WISC-III administration impossible to complete.

Mean t-IQ score was lower in area A than in area B children by approximately 18 points (92.1 ± 7.8 *vs.* 110 ± 10, $P < 0.00005$).

When we compared the intelligence test results of the ADHD+ve, ADHD−ve, and control children (Table 2), we observed that t-IQ score was lower in ADHD+ve than in ADHD−ve children by 11 points; and in both subgroups, it was lower than in the control group by 22 and 11 points, respectively. The attention WISC-III freedom-from-distractibility subscore was lower only in ADHD+ve children than in the controls, whereas the WISC-III verbal IQ subscore was lower in ADHD+ve than in either ADHD−ve or control children (14.4 and 21.4 points, respectively). The WISC-III

performance IQ subscore was lower in both ADHD+ve children and ADHD−ve children than in controls by 19.3 and 12.5 points, respectively.

Of the ADHD+ve children, three of 10 had a t-IQ score $\geq$ 90, six of 10 ranged between 90 and 75, and only one of 10 had a score less than 75. Both the ADHD−ve and the control children had a t-IQ score more than 90.

Maternal thyroid function and psychoneurological impairment

For the purposes of our study, we compared the changes in maternal thyroid function of both ADHD+ve (n = 11) and ADHD−ve (n = 5) area A subgroups with those of the control area mothers (n = 11) over the first half of gestation.

Average values of maternal T_3, T_4, FT_3, FT_4, TSH, and TBG saturation by T_4 at 8, 13, and 20 wk of gestation, in both area A ADHD+ve and ADHD−ve subgroups and in area B control mothers, are illustrated in Fig. 1.

Neither difference nor significant changes were observed at any time in serum total T_3 levels among the three groups. Serum FT_3 levels progressively dropped in both ADHD+ve and ADHD−ve subgroups by almost 20% at midgestation (F = 9.5, $P < 0.005$; and F = 8.4, $P < 0.05$, respectively), related to pregnancy progression (r = 0.55, $P < 0.001$; and r = 0.59, $P < 0.05$, respectively). Serum total T_4 values increased about 10% at the 13th wk in all three groups and remained at a plateau until midgestation. TBG saturation by T_4 was lower

TABLE 2. Neuropsychological test scores in ADHD+ve and ADHD−ve children from iodine-deficient area (area A) as compared with iodine-sufficient matched children (area B)

Neuropsychological test	Area A ADHD+ve children (n = 10)[a]	Area A ADHD−ve children (n = 5)	Area B control children (n = 11)	P value
Intelligence WISC-III full-scale IQ score (t-IQ)	88.0 ± 6.9	99.0 ± 2.0	110 ± 10	$<0.0001^b$ $<0.05^c$ $<0.005^d$
WISC-III freedom-from-distractibility score	8.8 ± 2.5	8.9 ± 2.5	10.3 ± 3.1	$<0.05^b$
WISC-III verbal IQ score	88.6 ± 11.4	103 ± 2.6	110 ± 12.3	$<0.001^b$ $<0.05^d$
WISC-III verbal section				
General information	9.0 ± 2.6	9.3 ± 3.0	9.6 ± 2.5	NS
General comprehension	7.6 ± 2.4	10.3 ± 2.9	10.9 ± 3.4	$<0.05^b$
Arithmetic	8.0 ± 1.5	10.6 ± 3.2	10.7 ± 2.1	$<0.005^b$ $<0.05^d$
Similarities	7.1 ± 4.9	11.3 ± 2.5	12.7 ± 2.9	$<0.05^b$
Vocabulary	9.1 ± 2.8	11.0 ± 2.0	14.2 ± 2.5	$<0.005^b$ $<0.05^d$
Digit span	9.7 ± 2.3	8.0 ± 2.6	9.1 ± 2.3	NS
WISC-III performance IQ score	87.8 ± 8.2	94.6 ± 7.1	107.1 ± 8.9	$<0.0001^b$ $<0.05^c$
WISC-III performance section				
Picture completion	5.9 ± 1.2	4.3 ± 2.3	11.3 ± 2.2	$<0.00001^b$ $<0.0005^c$
Picture arrangement	9.0 ± 2.4	11.0 ± 3.6	10.5 ± 1.7	NS
Block design	9.5 ± 3.2	8.7 ± 1.5	11.4 ± 1.9	$<0.05^c$
Object assembly	9.5 ± 5.0	14.6 ± 3.5	11.1 ± 2.5	$<0.05^c$
Coding	8.7 ± 3.4	8.0 ± 1.0	11.0 ± 4.3	NS
Mazes	8.7 ± 2.6	5.3 ± 3.5	11.0 ± 2.8	$<0.05^b$ $<0.01^c$

NS, Not significant.
[a] Results refer to 10/11 ADHD+ve children due to the fact that in 1/11, extreme inattention and hyperactivity made WISC administration impossible.
[b] ADHD+ve *vs.* controls.
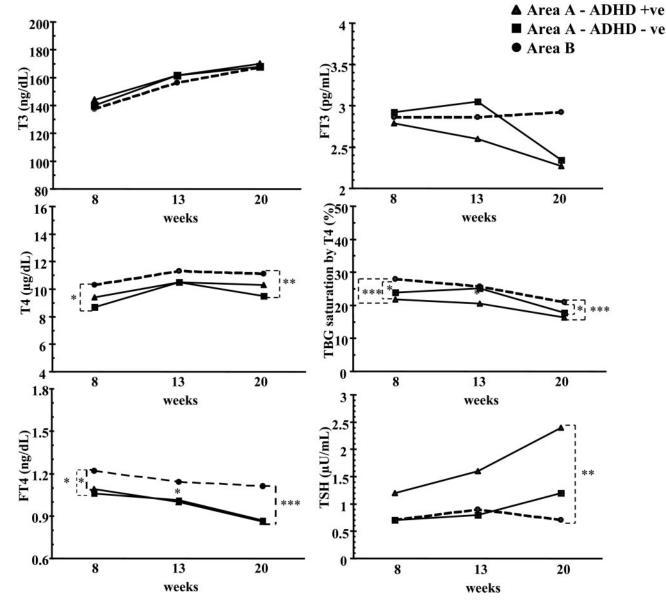[c] ADHD−ve *vs.* controls.
[d] ADHD+ve *vs.* ADHD−ve.

FIG. 1. Average values of maternal T_3, T_4, FT_3, FT_4, TSH, and TBG saturation by T_4 at 8, 13, and 20 wk of gestation in both area A ADHD+ve and ADHD−ve subgroups and in area B control mothers. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.005$.

in both ADHD+ve and ADHD−ve subgroups than in the area B mothers (t = 3.1 and 2.0, respectively) from the 8th wk onwards and further declined by about 25% with pregnancy progression (r = 0.39, $P < 0.05$; and r = 0.63, $P < 0.05$, respectively), ultimately remaining lower in both A subgroups than in the area B mothers (t = 3.27 and 1.97, respectively) at midgestation. Serum FT_4 values decreased by about 20% with gestational age in both A subgroups (r = 0.44, $P = 0.01$; r = 0.76, $P < 0.001$, respectively) but by only 8% in the control area, being always lower in both ADHD+ve and ADHD−ve subgroups than in area B pregnant women at any time (t = 1.8 and 2.6, respectively, at 8 wk; t = 2.17 and 1.98 at 13 wk; t = 3.0 and 3.57 at 20 wk). Serum TSH mean values increased over the first half of gestation about 100% (F = 4.9, $P < 0.05$) in the ADHD+ve subgroup and about 30% (F = 10.5, $P < 0.01$) in the ADHD−ve subgroup, remaining un-

modified in the control mothers. At 20 wk, TSH levels were higher in the ADHD+ve subgroup than in the control area (t = 2.4).

Figure 2 shows individual maternal FT_4 and TSH data for both area A and area B subgroups. Of the 16 area A women, eight had serum FT_4 values that were lower than normal for the gestational week. In fact, hypothyroxinemia occurred at 8 wk in one ADHD+ve mother, at 13 wk in two other ADHD+ve mothers, and at 20 wk in one ADHD−ve and in four more ADHD+ve mother**s.** In two of these eight women, hypothyroxinemia was accompanied by a slight increase in TSH concentration, one from the second sampling on and the other at 20 wk. In the mothers from area B, both FT_4 and TSH values were consistently found to fall within the normal range in all but one woman, who was found (at the 13th wk of gestation) to be transiently hypothyroxinemic.
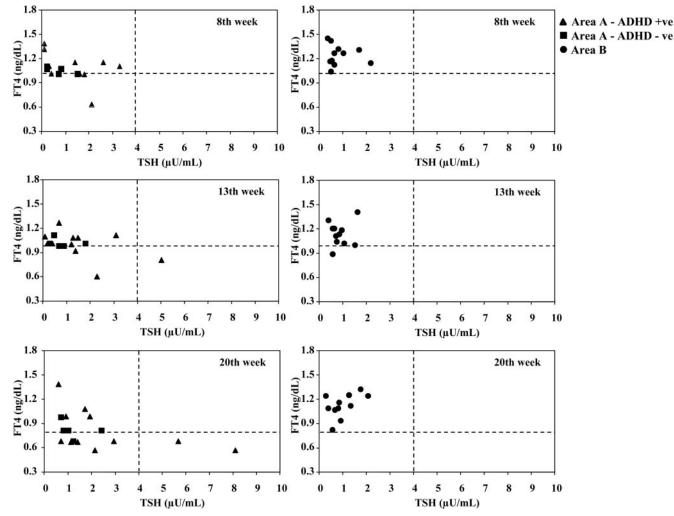
FIG. 2. Serum FT_4 and TSH levels in the 16 area A studied mothers (n = 11 ADHD+ve and n = 5 ADHD−ve subgroups) (*left*) and in the 11 area B pregnant women (*right*) measured at 8, 13, and 20 wk of gestation. The *vertical dotted lines* indicate the highest normal TSH value (4.0 μU/ml). The *horizontal dotted lines* indicate the lowest normal FT_4 values for the gestational week [1.02 ng/dl (13.1 pmol/liter) at 8 wk, 0.98 ng/dl (12.7 pmol/liter) at 13 wk, and 0.85 ng/dl (11.0 pmol/liter) at 20 wk].

Therefore, thyroid failure occurred in early pregnancy in eight of the 16 (50%) women from the ID area and only transiently in one of 11 (9.1%) from the control area.

Seven of eight (87.5%) women who experienced hypothyroxinemia during early gestation generated seven of the 11 ADHD+ve children, whereas the remaining four of 11 were born to mothers who remained euthyroid throughout the first half of their pregnancies. Conversely, of the five ADHD−ve children, four (80%) were born to mothers who had remained euthyroid throughout the study period, whereas only one was born to a hypothyroxinemic mother.

Finally, of the 11 of 16 area A children with neuropsychological disorders, seven of 11 (63.6%) were born to the eight iodine-deficient women who had become hypothyroxinemic during early gestation. As a consequence, the overall prevalence of ADHD among the area A children studied was significantly higher (χ^2, 2.34; $P = 0.001$) in children born to mothers whose FT_4 concentration was below the reference range at midgestation.

Similarly, the children's t-IQ score was directly ($r = 0.56$, $P < 0.005$) related to maternal FT_4 and inversely ($r = 0.63$, $P <$

0.001) related to maternal TSH values at midgestation, when both area A and B were considered as a whole (Fig. 3).
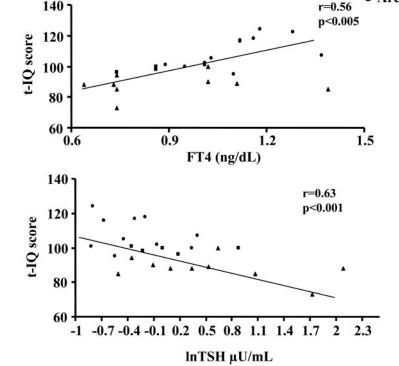
Discussion

ADHD is a developmental disorder involving difficulties with sustained attention, distractibility, poor impulse control, and hyperactivity or inability to regulate activity level to situational demands. The disorder is believed to arise early in childhood (3–7 yr) and is considered organic in pathology (12). The current view is that dysfunctions of both the frontal and prefrontal lobes and of cortical and subcortical striatal areas, involved in impulsivity and motor activity control (13) and in inhibition of irrelevant responses and executive functions (14), respectively, are responsible for the disorder
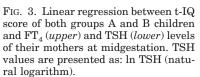
A high prevalence (70%) of ADHD has been reported in children with GRTH (4), a disease caused by mutations in the thyroid receptor-β gene and characterized by reduced responsiveness of peripheral and pituitary tissues to the actions of the thyroid hormone.

The present study was based on long-term observation of

FIG. 3. Linear regression between t-IQ score of both groups A and B children and FT_4 (*upper*) and TSH (*lower*) levels of their mothers at midgestation. TSH values are presented as: ln TSH (natural logarithm).

the neuropsychological and intelligence performances of children born to mothers from a mild-moderate ID area, some of whom developed hypothyroxinemia during early pregnancy. At the time of initial neurological observation, we reported clinical findings that were consistent with a diagnosis of ADHD, but we were not able to confirm this suspicion because the children studied were thought to be still too young (18–36 months). It was for this reason that we prolonged our observation until the children were 8–10 yr old, when conclusive diagnosis of ADHD was made in 11 of 16 (68.7%) children born to mothers from this mild-moderate ID area in whom the disorder was associated with some degree of intelligence failure. In fact, ADHD+ve children's mean IQ scores (although $\geq$75 points in all but one) were 12 and 23 points lower than those of the ADHD−ve and control children, respectively.

When neurological results were related to early-pregnancy maternal thyroid function, it was seen that all 11 ADHD+ve children were born to ID area mothers whose thyroid function proved more heavily compromised than that of the five ADHD−ve mothers and that seven of eight (87.5%) ID area mothers who experienced thyroid failure generated ADHD+ve children. It is worth noting, however, that individual TSH levels fell consistently within the normal range in all but two of these women, whose TSH concentration slightly increased toward the end of the study period. Therefore, most of the ADHD+ve children (seven of 11) were born to mothers who had become hypothyroxinemic during early gestation, whereas four of five (80%) ADHD−ve children were born to mothers who remained consistently euthyroid during the first half of gestation.

The ADHD prevalence of almost 70% in our ID area (rising to 87.5% in hypothyroxinemic mothers), so surprisingly similar to that reported in children with GRTH, seems to point to a strong association of this neuropsychological disorder with both the GRTH syndrome and the ID-induced early gestation maternal hypothyroxinemia. ADHD syndrome associated with GRTH could be the result of the developing brain being deprived of the biological effect of the thyroid hormone, whereas ADHD in children from our ID area could be due to an inadequate supply of maternal thyroid hormone to the fetal brain, development of which therefore suffered from varying (and subtle) degrees of maternal thyroid failure during the first phases of organogenesis.

The role of T_4 transfer in human beings in early pregnancy is key to ensuring the normal neurological development of the fetus, which is particularly important before the onset of thyroid hormone secretion by the fetal thyroid (15) (20th wk). The existence of T_4 transfer from mother to fetus has been demonstrated by several conclusive studies in both rats (16–21) and human beings (22). First-trimester fetal tissues are exposed to concentrations of FT_4, which have recently been demonstrated in human fetuses to ultimately depend on the circulating maternal levels of T_4 or FT_4 (23).

The relationship between maternal thyroid hormone deficiency and neurological damage in offspring has already been established by several epidemiological studies in areas with severe ID (24) or normal dietary iodine intake (25, 26) and in animal models (27–28). Maternal hypothyroxinemia, also observed in areas with adequate iodine intake, has been regarded, so far, as a normal condition, even though reduced intellectual performances have been reported in children

born to iodine-sufficient hypothyroxinemic mothers (29). The growing concern that hypothyroxinemia during early gestation could be harmful to the fetus (30–32) has recently been reinforced by the first experimental evidence of a permanent alteration of cortical cytoarchitecture in the progeny of ID-induced hypothyroxinemic dams (33).

In conclusion and for the first time in a mild-moderate ID area, our data seem to vindicate the hypothesis of a direct causal relationship between ID-induced early gestational maternal hypothyroxinemia and ADHD, which might therefore be considered as a new ID disorder to be systematically screened in the progeny. A recent report indicating that neuropsychological development does not seem to be adversely affected in children whose maternal hypothyroxinemia is corrected within the 24th wk of pregnancy (34) is a strong indication of the need for routine screening and monitoring of thyroid function in early pregnancy. An inadequate dietary supply of iodine, still a widespread problem all over the world (including European countries and the United States) (32), further emphasizes the need for intensive programs of iodine prophylaxis to promptly prevent/correct gestational hypothyroxinemia and the resulting permanent and invalidating neurological damage to progeny.

Acknowledgments

References

1. **Vermiglio F, Sidoti M, Finocchiaro MD, Battiato S, Lo Presti VP, Benvenga S, Trimarchi F** 1990 Defective neuromotor and cognitive ability in iodine-deficient schoolchildren of an endemic goiter region in Sicily. J Clin Endocrinol Metab 70:379–384
2. **Vermiglio F, Lo Presti VP, Scaffidi Argentina G, Finocchiaro MD, Gullo D, Squatrito S, Trimarchi F** 1995 Maternal hypothyroxinemia during the first half of gestation in an iodine deficient area with endemic cretinism and related disorders. Clin Endocrinol (Oxf) 42:409–415
3. **Vermiglio F, Lo Presti VP, Castagna MG, Violi MA, Moleti M, Finocchiaro MD, Mattina F, Artemisia A, Trimarchi F** 1999 Increased risk of maternal thyroid failure with pregnancy progression in an iodine deficient area with major iodine deficiency disorders. Thyroid 9:19–24
4. **Hauser P, Zametkin AJ, Martinez P, Vitiello B, Matochik JA, Mixson AJ, Weintraub BD** 1993 Attention deficit-hyperactivity disorder in people with generalized resistance to thyroid hormone. N Engl J Med 328:997–1001
5. **Pearl PL, Weiss RE, Stein MA** 2001 Medical mimics. Medical and neurological conditions simulating ADHD. Ann NY Acad Sci 931:97–112
6. **Touwen Bert CL** 1979 Examination of the child with minor neurological dysfunction. Clinics. In: Developmental Medicine 71. London: Spastic International Medical Publications
7. **American Psychiatric Association** 2000 DSM-IV-TR. Diagnostic and statistical manual of mental disorders. 4th ed. Text revision, Washington DC: American Psychiatric Press; 78–85
8. **Marzocchi GM, Cornoldi C** 1999 In: Vio C, Marzocchi G, Offredi F, eds. Il bambino con deficit di attenzione/iperattività. Trieste, Italy: Erickson; 11–25
9. **Marzocchi GM, Cornoldi C** 1991 Wechsler intelligence scale for children. 3rd ed. San Antonio, TX: Psychological
10. **Luckasson R, Coulter DL, Polloway EA, Reiss S, Schalock RL, Snell ME, Spitalnik DM, Stard JA,** eds. 1992 Mental retardation: definition, classification and systems of support. Washington DC: American Association of Mental Retardation
11. **DeLong GR, Stanbury JB, Fierro-Benitez R** 1985 Neurological signs in congenital iodine deficiency disorder (endemic cretinism). Dev Med Child Neurol 27:317–324
12. **Barkley RA** 1997 Attention-deficit/hyperactivity disorder, self-regulation, and time: toward a more comprehensive theory. J Dev Behav Pediatr 18:271–279
13. **Hind GW, Riccio CA, Cohen MJ, Gonzalez JJ** 1991 Neurological basis of attention deficit hyperactivity disorder. Except Child 60:118–124
14. **Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, Sarfatti SE, Vauss YC, Snell JW, Lange N, Kaysen D, Krain AL, Ritchie GF, Rajapakse JC, Rapoport JL** 1996 Quantitative brain magnetic resonance imaging in ADHD. Arch Gen Psychiatry 53:607–616
15. **Morreale de Escobar G, Pastor R, Obregon MJ, Escobar del Rey F** 1985 Effects of maternal hypothyroidism on the weight and thyroid hormone content of rat embryonic tissues. Endocrinology 117:1890–1901
16. **Sweney LR, Shapiro BL** 1975 Thyroxine and palatal development in rat embryos. Dev Biol 42:19–27
17. **Obregon MJ, Mallol J, Pastor R, Morreale de Escobar G, Escobar del Rey F** 1984 L-Thyroxine and 3,3′,5-triiodo-L-thyronine in rat embryos before onset of foetal thyroid function. Endocrinology 114:305–307
18. **Woods RJ, Sinha AK, Ekins RP** 1984 Uptake and metabolism of thyroid hormones by the rat foetus in early pregnancy. Clin Sci (Lond) 67:359–363
19. **Morreale de Escobar G, Obregon MJ, Ruiz de Ona C, Escobar del Rey F** 1989 Comparison of maternal to foetal transfer of 3-5-5′-triiodo-L-thyronine versus thyroxine in rats, as assessed from 3-5-5′-triiodo-L-thyronine levels in foetal tissues. Acta Endocrinol (Copenh) 120:20–30
20. **Calvo R, Obregon MJ, Ruiz de Ona C, Escobar del Rey F, Morreale de Escobar G** 1990 Congenital hypothyroidism, as studied in rats. Crucial role of maternal thyroxine but not of 3-5-5′-triiodothyronine in the protection of the foetal brain. J Clin Invest 86:889–899
21. **Morreale de Escobar G, Calvo R, Obregon MJ, Escobar del Rey F** 1990 Contribution of maternal thyroxine to foetal thyroxine pools in normal rats near term. Endocrinology 126:2765–2767
22. **Vulsma T, Gons MH, De Vijlder JJ** 1989 Maternal-foetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. N Engl J Med 321:13–16
23. **Calvo RM, Jauniaux E, Gulbis B, Asuncion M, Gervy C, Contempre B, Morreale de Escobar G** 2002 Foetal tissues are exposed to biologically relevant free thyroxine concentration during early phases of development. J Clin Endocrinol Metab 87:1768–1777
24. **Delange F** 1994 The disorders induced by iodine deficiency. Thyroid 4:107–128
25. **Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ** 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341:549–555
26. **Glinoer D** 1997 The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 18:404–433
27. **Friedhoff AJ, Miller JC, Armour M, Schweitzer JW, Mohan S** 2000 Role of maternal biochemistry in foetal brain development: effect of maternal thyroidectomy on behaviour and biogenic amine metabolism in rat progeny. Int J Neuropsychopharmacol 3:89–97
28. **Dowling ALS, Martz GU, Leonard JL, Zoeller RT** 2000 Acute changes in maternal thyroid hormone induce rapid and transient changes in specific gene expression in foetal rat brain. J Neurosci 20:2255–2265
29. **Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL** 1999 Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf) 50:149–155
30. **Morreale de Escobar G, Obregon MJ, Escobar del Rey F** 2000 Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia? J Clin Endocrinol Metab 85:3975–3987
31. **Pop VJ, van Baar AL, Vulsma T** 1999 Should all pregnant women be screened for hypothyroidism? Lancet 354:1224–1225
32. **Utiger RD** 1999 Maternal hypothyroidism and foetal development. N Engl J Med 34:601–602
33. **Lavado-Autric R, Auso E, Garcia-Velasco JV, Arufe Mdel C, Escobar del Rey F, Berbel P, Morreale de Escobar G** 2003 Early maternal hypothyroxinemia alters histogenesis and cerebral cortex cytoarchitecture of the progeny. J Clin Invest 111:1073–1082
34. **Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ** 2003 Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow up study. Clin Endocrinol (Oxf) 59:282–288