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The changing phenotype of iodine deficiency disorders: a review of thirty-five years of research in north-eastern Sicily

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Abstract
Iodine deficiency disorders (IDD) still represent a major public health problem, with almost 30% of the world population being exposed to the consequences of nutritional iodine deficiency (ID). In Italy, despite a sustained policy of iodine prophylaxis, more than 10% of people is still affected with goiter, and a presumably higher rate of subjects may suffer from minor cognitive deficits due to inadequate iodine supply during antenatal life. This review of systematic observational studies carried out over thirty-five years (1980-2015) in a sentinel ID area in North-eastern Sicily highlights the changing phenotypes of IDD in this region. Over the years profound improvements in nutritional iodine status in North-eastern Sicily has occurred, due to both silent and active iodine prophylaxis. Endemic cretinism, resulting from severe iodine deficiency, has been progressively replaced by less serious deficits of intellectual and cognitive abilities, which nevertheless deserve proper attention.

Key words
- iodine
- iodized salt
- endemic cretinism
- cognitive deficits

INTRODUCTION

Several lines of evidence have accumulated over the past 20 years, collectively demonstrating the importance of thyroid hormone (TH) in regulating fetal neurodevelopment [1-8]. Prior to the onset of fetal thyroid function, the mother is the only source of thyroid hormone for the developing brain. By weeks 16-20 post-conception, fetal thyroid gland development has occurred, and from this point onwards both the mother and fetus cooperate to make-up the fetal thyroid hormone pool [6]. Any impairment of maternal and fetal thyroid function, occurring either independently or concomitantly, can result in brain damages and major or minor neuro-intellectual disorders in the offspring, the severity of which being dependent on the magnitude and length of TH deprivation, as well as on fetal age [9, 10].

Iodine deficiency (ID) still represents the most preventable cause of both maternal and fetal thyroid insufficiency [11, 12]. The World Health Organization (WHO) recommends that pregnant women receive a daily iodine intake of 250 µg [13]. When this goal is not achieved, iodine intake is considered insufficient to prevent neuro-intellectual disorders.

Over more than 30 years, ID disorders (IDD) affecting people living in northeastern Sicily have been extensively studied, recorded and monitored. Iodine nutrition, which was severely deficient in the '80s, progressively improved, as a result of the silent iodine prophylaxis [14, 15], and more recently of a systematic and effective policy of iodine prophylaxis, mostly based on implementation of iodized salt consumption by households [16-18]. Nonetheless, non systematic epidemiological data show iodine intake in this area to be less than adequate, and ID-related minor neurointellectual disorders still present. Focusing on how these disorders have been changing with the progressively improvement of iodine nutrition status in local population is the objective of the present review.

EPIDEMIOLOGICAL AND CLINICAL CHARACTERISTICS OF THE STUDIED AREA

The first epidemiological characterization of IDD in different Sicilian areas was provided by Delange *et al.* in 1978 [19]. At that time, those areas were approaching the severe iodine deficiency, since daily urinary iodine excretion (UIE) and goiter prevalence in schoolchildren were almost 25 µg/day and 50%, respectively. Moreover, endemic cretinism (myxedematous variant included) was known to be present in the same area. Since then, changes in the prevalence of IDD have occurred over almost 3 decades, mostly due to the improved distribu-

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tion network of frozen foods, including sea foods, and of industrially prepared dairy products, finally resulting in a progressive and "silent" increase in daily dietary iodine intake [14]. In addition, starting from 2005, iodine prophylaxis was implemented in Italy in the context of a nationwide program, by means of salt iodization [20]. Improvement in iodine nutrition status of local population resulted in a significant increase in UIE (from 62.2 ± 38.2 µg/L in 2000-2007 to 95.6 ± 25.8 µg/L in 2012-2013), as well as in a decrease of goiter prevalence (from 16.3% in 2000-2007 to 7.6% in 2012-2013) in schoolchildren [21].

PHENOTYPES OF ID-RELATED NEUROINTELLECTUAL DISORDERS: FROM ENDEMIC CRETINISM TO "MINOR" NEUROLOGICAL DISORDERS

The spectrum of neurological disorders described in the endemic goiter areas in Sicily over the years encompasses severe clinical manifestations of ID, from endemic cretinism to subtle cognitive deficits, still present in some areas *(Table 1)*.

Endemic cretinism

In 1981 [22] and 1990 [23], we described typical characteristics of endemic cretinism in an area characterized by an even distribution of neurological, myxedematous and mixed clinical variants. The correlation of the three phenotypes to the birthdates of the affected subjects revealed that cretins born from 1970 onwards were affected exclusively with the neurological variant. This observation suggested the myxedematous forms, only observed in older subjects, to be the result of a more severe degree of iodine deficiency over a protracted period, and therefore affecting intrauterine life, (neurological damage), infancy, childhood, adolescence and adult life (myxedematous features) [23].

Endemic cognitive deficit (ECD)

Subsequent non systematic observational studies carried out in the same areas revealed that, far from being iodine sufficiency achieved, no more subjects affected with endemic cretinism were born starting from the '80s. However, a systematic study on prepubertal primary schoolchildren living in two iodine deficient areas within the same region and in age-matched schoolchildren from an iodine sufficient (IS) area, revealed the presence of defective or borderline performances in visual-perceptual and motor abilities in almost 14% and 17% ID schoolchildren, respectively, *vs* 3.5% in the control group [24]. The disorder, defined endemic cognitive deficiency (ECD), was associated in one third of affected children to neurosensorial and neuromuscular abnormalities (disturbances in standing and gait, dyslalia, impaired hearing and deaf-mutism, increased tendon reflexes, clonus of the foot, Babinski sign), overall suggestive of a much less severe phenotype of endemic cretinism. Moreover, the vast majority of ECD children and more than half borderline children scored at intelligence quotient (IQ) testing less than 90 points. Interestingly and at variance with endemic cretins, children affected with ECD were clinically and biochemically euthyroid. This observation raised the question whether abnormality in thyroid function suffered by either expectant mothers or foetuses during gestation might account for ECD or other neurological disorders affecting the (euthyroid) progeny. This issue was addressed in two systematic studies evaluating changes of maternal thyroid function over gestation. Overall, these studies demonstrated a clear and progressive decline in

Table 1
Overview of clinical and epidemiological studies carried out in ID areas in north-eastern Sicily from 1978 to 2016

Year	Ref	Main findings
1978	[19]	Epidemiological characterization of IDD in different Sicilian areas, including the description of myxedematous variant of endemic cretinism. Median UIE: 25 µg/day; prevalence of goiter in schoolchildren > 50%
1989	[14]	"Silent" iodine prophylaxis improves nutritional iodine status in general population: median UIE: 45 µg/day; prevalence of goiter in schoolchildren 26.5-44%[a]
1990	[23]	Estimated prevalence of endemic cretinism in the general population in two ID areas in north-eastern Sicily: 0.13%. Description of 22 cretins living in the same ID areas showing either myxedematous, neurological or combined features of endemic cretinism
1990	[25]	Description of a novel IDD (endemic cognitive deficit, ECD) characterized by defective IQ associated with neurosensorial and neromuscolar abnormalities, affecting 14% of apparently normal schoolchildren
1995 and 1999	[26, 27]	Evidence of high prevalence of maternal thyroid failure during gestation (50% at midgestation and 70% at pregnancy term)
2004	[28]	ADHD diagnosed in almost 90% offspring of mothers exposed to mild-moderate ID during pregnancy and experiencing transient isolated hypothyroxinemia during the first half of gestation. Mean (± SD) UIE 62.2 ± 38.2 µg/L; prevalence of goiter in schoolchildren 16.3%
2008	[17]	Prolonged use of iodized salt associated with a significantly reduced risk of maternal thyroid insufficiency during pregnancy (36.8% *vs* 6.4%; P 0.0005; relative risk 5.7, P 0.001)
2016	[21]	Threefold higher prevalence of decreased neurocognitive test outcomes among children of unsupplemented mothers than among children born to mothers regularly consuming iodized salt (OR ~ 8 (95% CI, 2.4 to 24.9). Mean (± SD) UIE 95.6 ± 25.8 µg/L; prevalence of goiter in schoolchildren 7.6%

ID: iodine deficiency; IDD: iodine deficiency disorders; UIE: urinary iodine excretion; IQ; intelligence quotient; ADHD: attention deficit and hyperactivity disorder; [a]: different municipalities.

maternal thyroid output with pregnancy progression, with 50% and 70% of women becoming hypothyroid at midgestation and at pregnancy term, respectively [25, 26]. It is of note that the decline in maternal serum free-thyroxine (FT4) concentrations throughout gestation observed in these women was almost double that reported by Glinoer [27] in Bruxelles (37% *vs* 20%), a trend which was mirrored by a halved median UIE in our population compared to the Belgian women. In other words, a direct relationship between maternal iodine status and gestational thyroid function was evident, and the more severe the iodine deficiency, the higher the prevalence of maternal thyroid failure.

Attention deficit hyperactivity disorders (ADHD)

Based on the evidence of the previously described ECD and the high prevalence of maternal thyroid failure, further neurobehavioral and psychomotor systematic screenings were carried out in children born to ID mothers. Preliminary observations, made when children were 18-36 months old, had unexpectedly revealed symptoms suggestive of hyperactivity. The possibility that those features might be the initial symptoms of attention deficit hyperactivity disorders (ADHD) prompted us to re-evaluate these children when they had reached primary school age. The final study included 16 children born to healthy mothers living in the above described ID area and 11 age-matched control children born to women from a marginally IS area [28]. In addition to neurological examination and ADHD screening, IQ by Wechsler Intelligence Scale for Children (WISC-III) [29, 30] was also measured. Neuromotor evaluation revealed no signs of neurological impairment in any of the children. However, 68% of the children born to ID mothers was diagnosed with ADHD, whereas none of the IS area children was affected with ADHD. In addition, total-IQ (t-IQ) score was lower in ADHD-positive (ADHD+ve) than in ADHD-negative (ADHD-ve) children by 11 points, and in both subgroups than in the control group by 22 and 11 points, respectively. Finally, neurological results were found to be related to early-pregnancy maternal thyroid function, in that 87.5% of ID area mothers who experienced thyroid failure generated ADHD+ve children. Similarly, the children's t-IQ score was directly ($r = 0.56$ $p < 0.005$) related to maternal FT4 and inversely ($r = 0.63$ $p < 0.001$) related to maternal TSH values at mid gestation. In conclusion, this study revealed, for the first time, the existence of a strong association between iodine deficiency and ADHD based on long-term observation of the neuropsychological and intelligence performances of children born to mothers from a mild-moderate ID area.

Defective verbal abilities

Alongside these and other studies [31-39] showing a strong association between maternal thyroid insufficiency and neurobehavioral disorders in offspring, other evidence has been produced over the years not confirming a causal relationship between the above mentioned events [40-46]. In particular, the absence of intellectual impairment among children born to mothers severely hypothyroid in early pregnancy has been reported from Japan [45, 46], and the only randomized clinical trial investigating the effects of correcting (mild) maternal thyroid insufficiency by means of levothyroxine (LT4) therapy did not show improved cognitive outcomes in their offspring [47]. High differences in iodine nutrition status of pregnant women included in the above studies might account for these conflicting results. In fact, studies demonstrating a relationship between maternal thyroid function and impaired intellectual outcome of the offspring were mostly conducted in ID areas. Similarly, the women in the study of Lazarus were from an area that, based on recent epidemiological surveys, may be classified as mildly ID [48]. Though thyroid insufficiency in these women was corrected by giving them LT4, their nutritional iodine intake was likely inadequate to guarantee fetal euthyroidism. Conversely, in the Japanese anecdotal case series [45, 46], despite the more severe maternal hypothyroidism, gestational nutritional iodine intake was more than adequate. All of this might suggest that gestational iodine status might play a more pivotal role than maternal thyroxinemia *per se* in determining neuro-intellectual outcomes in progeny, likely by providing the fetus with adequate iodine amounts for his own thyroid hormone production. To examine whether iodine status of mothers or their thyroxinemia affects mental development of their children, we designed a pilot prospective observational study involving school-age children born to women who had been using iodized salt long before becoming pregnant (supplemented mothers) with that of children born to women never using it (unsupplemented mothers). A further stratification based on maternal LT4 treatment, uninterruptedly given prior to and during pregnancy, either in association or not with iodized salt consumption, eventually allowed us to weigh up the effect of maternal nutritional iodine status against maternal thyroxinemia on cognitive outcome in the progeny. The primary outcomes were IQ tests (verbal, performance, and full-scale) performed in their children [21]. This study showed that, irrespective of LT4 treatment given to their mothers, children born to iodine-supplemented mothers had higher IQ scores than those born to unsupplemented mothers (14, 10, and 13 points for verbal, performance, and t-IQ tests, respectively). Moreover, a threefold higher prevalence of decreased neurocognitive test outcomes was found among children of unsupplemented mothers than among children born to mothers who consumed iodized salt, this difference corresponding to an odds ratio of nearly 8 (95% CI, 2.4 to 24.9) [21]. Thus, this study indicates that a significant improvement in IQ scores may be achieved by optimizing maternal iodine nutrition during preconception and pregnancy, and that it is largely independent of maternal FT4 levels. This being the case, neurodevelopment may be more dependent on fetal than maternal thyroid function, and the less favourable cognitive outcomes observed in infants of unsupplemented mothers might be the result of the exposure of the developing brain to insufficient fetal TH levels, as a consequence of a low iodine availability. Interestingly, in our series of children verbal abilities were found to be more heavily affected,

with significant differences between verbal IQ (VIQ) and performance IQ found in children of unsupplemented mothers only. In addition, a significant association between low maternal urinary iodine and defective VIQ was found. Overall, these findings are in keeping with others recently reported. The Avon Longitudinal Study of Parents and Children in the United Kingdom [49] showed that children born to mothers exposed to iodine deficiency during pregnancy were more likely to have lower VIQ and reading scores as compared with the children born to iodine sufficient mothers. Also, in a retrospective analysis of almost five-hundred mother-child pairs, Taylor et al. showed that maternal perchlorate levels in the highest 10% of the population increased the odds of offspring IQ < 80, with a greater negative impact observed on VIQ than PIQ [50]. The link between impaired verbal abilities and inadequate fetal iodine availability is presently unknown. However, a relatively low VIQ may be related to central auditory processing disorders (cAPDs) [51, 52]. These disorders are not associated to peripheral hearing defects, and result from difficulties in the perceptual processing of auditory information in the central nervous system. Causes of cAPDs may include misplaced cells in the auditory cortical areas and/or delay in myelin maturation [53, 54], both neurodevelopmental events known to be TH regulated [7]. Interestingly, cAPDs cover a wide range of behavioral disorders, including ADHD among others [55].

MATERNAL THYROID FUNCTION AND IODINE PROPHYLAXIS PROGRAMS

The evidence of minor neurointellectual disorders in schoolchildren living in the studied area prompted us to promote in 2003 a local program of iodine prophylaxis on a voluntary basis, encouraging iodized salt consumption in women of child-bearing age and pregnant women living in the ID area where the aforementioned studies had been carried out. The program also included the monitoring of thyroid function over gestation and was aimed at early detection/correction of maternal thyroid underfunction, and ultimately prevent neurointellectual disorders in children. The efficacy of iodine prophylaxis using iodized salt in preventing maternal thyroid failure over gestation was prospectively evaluated in a study involving one hundred consecutive thyroperoxidase antibody-negative pregnant women, two third of whom had regularly used iodized salt for at least 2 years prior to becoming pregnant and the remaining who commenced iodized salt consumption upon becoming pregnant [17]. This study showed that, compared to short-term iodine prophylaxis, prolonged use of iodized salt was associated with a significantly reduced risk of maternal thyroid insufficiency during pregnancy (36.8% *vs* 6.4%; *P* 0.0005; relative risk 5.7, *P* 0.001), likely because of the greater replenishment of intra-thyroidal iodine stores. However, even in the women who had been consuming iodized salt for a long period prior to pregnancy, median UIE at recruitment was indicative of inadequate iodine intake for pregnancy (115 μg/liter, consistent with an estimated daily iodine intake of about 190 μg). In addition, a high prevalence of maternal thyroid failure in women living in the same area was confirmed in a subsequent study [56]. For these reasons, we launched a further information and awareness campaign urging general practitioners, gynaecologists and endocrinologists to advise locally resident pregnant women to use, in addition to iodized salt, iodine-containing supplements. The efficacy of this method of iodine prophylaxis in guaranteeing adequate maternal thyroid hormone levels throughout gestation was then investigated [57]. The thyroid function of 168 women who had received prenatal preparations containing 150 μg of iodine from early pregnancy was compared with that of either 105 women who had regularly used (> 2 yrs) iodized salt prior to becoming pregnant or 160 women who had neither taken iodine supplements nor used iodized salt. Overall, the regular use of iodine-containing supplements proved effective to the same extent of long-term iodized salt consumption in reducing the risk of inappropriately low FT4 levels during pregnancy. Notably, women given iodine-containing supplements experienced a transient, although significant, increase in TSH levels, mostly occurring 4-6 weeks after iodine supplementation had been introduced. We speculated that this effect was a sort of transient stunning effect on the thyroid gland, due to the activation of autoregulatory mechanisms of iodine metabolism of even physiological amounts of iodine (150 μg/day) within a chronically iodine-deprived thyroid gland.

It is of note that the spectrum of maternal thyroid function disorders changed over the years, with isolated maternal hypothyroxinemia progressively becoming the more frequent manifestation of maternal thyroid insufficiency and, conversely, overt hypothyroidism occurring only seldom [56]. Isolated hypothyroxinemia is characterized by low free-thyroxine levels, in the presence of TSH concentrations which fall within the normal range [10, 58]. This condition is assumed to be the result of an adaptive mechanism of maternal thyroid to inadequate iodine supply, and consists of a preferential triiodothyronine (T3) synthesis and secretion over thyroxine, ultimately aimed at sparing iodine. In such circumstances, circulating T3 is normal (or even slightly over the upper limit), and triggers negative feedback on pituitary TSH secretion, the concentrations of which fall within the normal range. As a result, the women are clinically euthyroid even when biochemically hypothyroxinemic. If the condition of inadequate iodine supply persists, this compensatory mechanism may fail because of the inability of the maternal iodine pool to guarantee even T3 production, and overt hypothyroidism thus occurs [10].

So far, maternal hypothyroxinemia, also observed in areas with adequate iodine intake, has been regarded as a normal condition, even though reduced intellectual performances have been reported in children born to iodine sufficient hypothyroxinemic mothers [34]. The growing concern that hypothyroxinemia during early gestation could be harmful to the fetus has also been reinforced by several clinical and experimental evidences [5, 10, 28, 34-39, 59-68]. Nonetheless, there is not unanimous consensus on whether women found to be hypothyroxinemic should be given levo-thyroxine to

compensate their low FT4 levels [69-71], although it has been recently suggested that LT4 therapy may be considered if isolated hypothyroxinemia is detected in the first trimester of pregnancy [72]. However, it should be noted that FT4 immunoassays currently available are essentially FT4 estimate tests that do not measure serum FT4 directly. While performing reasonably well in non-pregnant conditions, these methods are known to be sensitive to alterations in binding proteins and interpretation of FT4 values in pregnant women requires method-specific ranges [73, 74].

Summarizing the above evidence, long-term (> 2 years) iodized salt consumption and iodine containing supplements are both effective in minimizing, though not in completely eliminating, the risk of maternal thyroid failure. Indeed, estimations of iodine nutrition under those circumstances indicate the daily iodine intake from either iodized salt or iodine supplements alone to be below the requirements of pregnancy. In this view, we believe that in areas of mild-moderate iodine deficiency, which include several European countries [75], there is even greater justification for recommending long-term iodine supplementation by means of both iodized salt and iodine-containing supplements of women of child-bearing age prior to becoming pregnant. Such a strategy would reasonably guarantee the accumulation of sufficient iodine stores to meet the needs of both mother and foetus.

Finally, due to the high prevalence of gestational thyroid disorders [72, 76, 77] we believe that screening of thyroid function should be offered to all women planning a pregnancy and to women already pregnant, as soon as gestation is ascertained. In addition, the diagnostic and therapeutic challenges related to the significant changes in thyroid economy during pregnancy [78], along with the severity of both obstetrical and post-natal complications of thyroid dysfunctions and related treatment [79-81], suggest the need to refer pregnant women diagnosed with thyroid diseases to specialized centers providing endocrinological and gynaecological expertise.

CONCLUSIONS

Over the last thirty years profound improvements in nutritional iodine status in north-eastern Sicily has occurred, due to both silent and active iodine prophylaxis. Based on recent data, mild iodine deficiency is still present in the region, and it is our hope that iodine sufficiency may be achieved in a next future by further implementation of iodine prophylaxis programs. The observed increase in iodine intake was mirrored by progressive changes in IDD phenotypes affecting local population. Endemic cretinism resulting from severe iodine deficiency has been progressively replaced by intellectual and cognitive deficits that, although far less serious, cannot be disregarded.

At present, in Italy, despite a sustained iodized salt program, only 50% of the general population regularly consumes iodized salt [82]. This being the case, a high percentage of women of child-bearing age is likely to have iodine levels that are inadequate for the increased needs during pregnancy.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of the study.

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