The role of iodine in brain development

François Delange
International Council for Control of Iodine Deficiency Disorders, 153 Avenue de la Fauconnerie, B-1170 Brussels, Belgium

I is required for the synthesis of thyroid hormones. These hormones, in turn, are required for brain development, which occurs during fetal and early postnatal life. The present paper reviews the impact of I deficiency (1) on thyroid function during pregnancy and in the neonate, and (2) on the intellectual development of infants and children. All extents of I deficiency (based on I intake (μg/d); mild 50–99, moderate 20–49, severe < 20) affect the thyroid function of the mother and neonate, and the mental development of the child. The damage increases with the extent of the deficiency, with overt endemic cretinism as the severest consequence. This syndrome combines irreversible mental retardation, neurological damage and thyroid failure. Maternal hypothyroxinaemia during early pregnancy is a key factor in the development of the neurological damage in the cretin. Se deficiency superimposed on I deficiency partly prevents the neurological damage, but precipitates severe hypothyroidism in cretins. I deficiency results in a global loss of 10–15 intellectual quotient points at a population level, and constitutes the world's greatest single cause of preventable brain damage and mental retardation.

Iodine: Selenium: Thyroid: Brain development: Mental retardation

I is required for the synthesis of thyroid hormones. Thyroid hormones in turn act by regulating the metabolic pattern of most cells of the organism. They also play a determining role in the process of early growth and development of most organs, especially that of the brain, which occurs in human subjects during the fetal and early postnatal life. Consequently, I deficiency, if severe enough to affect thyroid hormone synthesis during this critical period, will result in hypothyroidism and brain damage. The clinical consequence will be mental retardation (Bernal & Nunez, 1995).

The recommended dietary allowance of I is (μg/d): 50 from 0 to 12 months; 90 from 1 to 6 years; 120 from 7 to 10 years; 150 during adolescence and adulthood; 200–300 during pregnancy and lactation (World Health Organization (WHO), 1996). When these physiological requirements are not met in a given population a series of functional and developmental abnormalities occur, including thyroid function abnormalities, and when I deficiency is severe, endemic goitre and cretinism, endemic mental retardation, decreased fertility rate, increased perinatal death and infant mortality occur. These complications, which constitute an hindrance to the development of the affected populations, are grouped under the general heading of I-deficiency disorders (Hetzel, 1983).

In 1990 1·6 billion individuals, i.e. 28·9 % of the global population, were at risk of I deficiency, which therefore appears as the greatest single cause worldwide of preventable brain damage and mental retardation (WHO/United Nations Children's Fund (UNICEF)/ International Council for Control of Iodine Deficiency Disorders (ICCIDD), 1994).

WHO/UNICEF/ICCIDD (1994) have defined three levels of severity of I deficiency, based on I intake (μg/d): mild 50–99; moderate 20–49; severe < 20.

The aim of the present paper is to review, for each of these three levels of deficiency, presently available data on:

(1) the impact of I deficiency on thyroid function in pregnant women and in neonates;
(2) the possible long-term consequences of I deficiency occurring during the critical period of brain development on the neuro-intellectual development of infants and children.

Abbreviations: ICCIDD, International Council for Control of Iodine Deficiency Disorders; RDC, the Democratic Republic of Congo; T_3, triiodothyronine; T_4, thyroxine; TSH, thyroid-stimulating hormone.

Corresponding author: Professor F. Delange, fax +32 2 675 18 98, email fdelange@ulb.ac.be

https://doi.org/10.1017/S0029665100000094 Published online by Cambridge University Press

Extensive reviews on these different aspects of I deficiency are available elsewhere (Burrow, 1972; De Long *et al*. 1989; Stanbury, 1994; Glinoer, 1997*a*; Stanbury *et al*. 1998).

Mild iodine deficiency

Thyroid function in the mothers

Under these conditions the serum levels of free thyroxine (T_4) decrease steadily during gestation (Glinoer 1997*a*,*b*). Although the median values remain within the normal range, one-third of the pregnant women have free T_4 values near or below the lower limit of the normal range. This picture is in clear contrast with the thyroid status during pregnancy in conditions of normal I intake, which is characterized by only a slight (15 %) decrease in free T_4 by the end of gestation.

After an initial reduction in serum thyroid-stimulating hormone (TSH) due to increased levels of human chorionic gonadotropin, serum TSH levels increase progressively in more than 80 % of the pregnant women, although these levels also remain within the normal range. This change is accompanied by an increase in serum thyroglobulin, which is directly related to the increase in TSH.

This situation of chronic thyroid hyperstimulation results in an increase in thyroid volume by 20–30 % during gestation, which is twofold higher than in conditions of normal I supply.

The role of the lack of I in the development of these different anomalies is indicated by the fact that daily supplementation with physiological doses of I (150 μg/d) prevents their occurrence (Glinoer *et al*. 1995).

Thyroid function in the neonates

Serum levels of TSH and thyroglobulin are higher in the neonates than in the mothers, indicating that neonates are more sensitive than adults to the effects of I deficiency (Glinoer 1997*a*). Again, the role of I deficiency is demonstrated by the fact that neonates born to mothers who have been supplemented with I during pregnancy have a lower thyroid volume and lower serum thyroglobulin levels, and higher urinary I levels than newborn infants born to untreated mothers (Glinoer *et al*. 1995).

Further evidence of chronic overstimulation of the neonatal thyroid by TSH is a slight shift towards elevated values for the frequency distribution of neonatal TSH on day 5, at the time of systematic screening for congenital hypothyroidism. The frequency of values above 5 mU/l blood is 4·5 % (Delange, 1998), while the normal value is below 3 % (WHO/UNICEF/ICCIDD, 1994).

Neuro-intellectual development

There is little evidence that the minor impairment of thyroid function observed in mothers and neonates in conditions of mild I deficiency markedly affects the intellectual development of the children. However, Aghini-Lombardi *et al*. (1995) reported that in children aged 6–10 years in an area in Tuscany with mild I deficiency (64 μg I/d) the reaction time is delayed as compared with matched controls from an I-sufficient area (142 μg I/d). The cognitive abilities of the children are not affected.

Moderate iodine deficiency

Thyroid function in the mothers

The anomalies are of the same nature but more marked than in conditions of mild I deficiency. For example, in an area of Sicily with an I intake of 40 μg/d, Vermiglio *et al*. (1995) reported a decline in levels of serum free T_4 of 31 % and a simultaneous increase in serum TSH of 50 % during early (8th–19th weeks) gestation.

Thyroid function in the neonates

Again the anomalies are of the same nature, but more drastic than in conditions of mild I deficiency. Transient effects of high levels of TSH or even transient neonatal hypothyroidism can occur. The frequency of the latter condition is approximately six times higher in Europe than in the USA where the I intake is much higher (Delange *et al*. 1983).

The shift of neonatal TSH towards elevated values is more marked and the frequency of occurrence of values above 20–25 mU/l blood, i.e. above the cut-off point used for recalling the neonates under suspicion of congenital hypothyroidism in programmes of systematic screening for congenital hypothyroidism, is increased. In Europe there is an inverse relationship between the median urinary I levels of populations of neonates, used as an index of their I intake, and the recall rate at screening (Delange, 1994).

It has to be pointed out that these changes in neonatal TSH frequently occur for levels of I deficiency which would not affect thyroid function in non-pregnant adults. The hypersensitivity of the neonates to the effects of I deficiency is explained by their very small intrathyroidal I pool, which requires increased TSH stimulation and a fast turnover rate in order to maintain normal secretion of thyroid hormones (Delange *et al*. 1993).

Based on these findings, it has been proposed that neonatal thyroid screening is used for monitoring the level of and correction of I deficiency (Delange, 1998).

Neuro-intellectual development

A large series of investigations conducted in areas with moderate I deficiency have demonstrated the presence of definite abnormalities in the psychoneuromotor and intellectual development of children and adults who are clinically euthyroid and who do not exhibit the other signs and symptoms of endemic cretinism, i.e. the most severe form of brain damage due to I deficiency. The psychometric tests used to demonstrate these abnormalities are various and include locally-adapted ‘culture-free’ intelligence tests. The findings include low visual–motor performances, motor skill, perceptual and neuromotor abilities, and low development quotients and intellectual quotients (for review, see De Long *et al*. 1989; Delange, 1994; Stanbury, 1994).

https://doi.org/10.1017/S0029665100000094 Published online by Cambridge University Press

Severe iodine deficiency

Thyroid function in the mothers

The most extensive available data on thyroid function during pregnancy in populations with an I intake below 25 μg/d are from New Guinea (Choufoer *et al*. 1965; Pharoah *et al*. 1984) and the Democratic Republic of Congo (RDC; former Zaire; Thilly *et al*. 1978; Delange *et al*. 1982).

The studies conducted in such environments show that the prevalence of goitre reaches peak values of up to 90 % in females of child-bearing age (Delange, 1994), and that during pregnancy serum T_4 is extremely low and serum TSH extremely high. However, it has been pointed out that in spite of a similar level of severe I deficiency in RDC and in New Guinea, serum T_4 in pregnant mothers is much higher in RDC (80 μg/l) than in New Guinea (30–50 μg/l; Morreale de Escobar *et al*. 1997). This discrepancy was understood only when it was demonstrated that in RDC I deficiency is aggravated by Se deficiency and thiocyanate overload (Delange *et al*. 1982; Vanderpas *et al*. 1990; Contempré *et al*. 1991; see p. 78).

Thyroid function in the neonates

As in the mother, the biochemical picture of neonatal hypothyroidism is characteristic, especially in RDC where mean cord serum T_4 and TSH are 74 μg/l and 70·7 μU/l respectively, and where as many as 11 % of the neonates have both a cord serum TSH above 100 μU/ml and the cord T_4 below 30 μg/l, i.e. a biochemical picture similar to that found in thyroid agenesis (Delange *et al*. 1993).

Neuro-intellectual development

Anomalies found in the 'normal' population are of the same type, although more frequent and more severe than those found in moderate I deficiency. The frequency distribution of intellectual quotients in children is shifted towards low values, when compared with matched controls who were not exposed to I deficiency during the critical period of brain development because of correction of the deficiency in the mothers before or during early gestation (Fierro-Benitez *et al*. 1974). More globally, in their meta-analysis of nineteen studies on neuromotor and cognitive functions in conditions of I deficiency, Bleichrodt & Born (1994) concluded that I deficiency results in a loss of 13·5 intellectual quotient points at the level of the global population. The delay in socio-economic development of populations exposed to I deficiency, a consequence of brain damage and loss of intellectual potential, is the reason why I deficiency, and not endemic goitre only, constitutes a major public health problem.

The most serious consequence of I deficiency on brain and physical development is endemic cretinism. Endemic cretinism is a polymorphous clinical entity defined essentially by severe and irreversible alterations in brain development, mental retardation and a combination of neurological signs including deaf mutism, squint, spastic diplegia, motor rigidity and shuffling gait, and of signs of severe thyroid insufficiency including dwarfism, myxoedema and sexual immaturity. The prevalence of cretinism can be as high as 15 % in severely-I-deficient populations. As a result of geographical differences in the epidemiological, clinical and biochemical features of the mentally- and physically-handicapped individuals known as endemic cretins, the definition of the syndrome was not clear, and resulted in vivid controversies until the aetiopathogenesis of the brain damage due to I deficiency was better understood (Boyages & Halpern, 1993; Delange, 2000).

Aetiopathogenesis of brain damage due to iodine deficiency during the perinatal period

The spectrum of the defects in brain development and neuro-intellectual performances resulting from I deficiency has to be interpreted on the basis of two recent sets of findings.

Roles of maternal, fetal and neonatal hypothyroxinaemia

Thyroid function and regulation are autonomous in mother and fetus. Until recently, it has been considered that they are also independent, because the transfer of thyroid hormones across the placenta, if any, is extremely limited (Fisher & Klein, 1981). In contrast, recent experimental and clinical data emphasize the importance of this transfer (for review, see Morreale de Escobar *et al*. 1997; Obregon *et al*. 1998). In the rat thyroid hormones are found in embryonic and fetal tissues before the onset of fetal thyroid function which occurs on day 18 of gestation. Nuclear receptors for triiodothyronine (T_3) are present in the fetus by 13 d of gestation and in the fetal brain by 14 d of gestation. The T_4 and T_3 available to early-stage embryos and fetuses are of maternal origin. At term 17·5 % of fetal extrathyroidal T_4 is still of maternal origin. These findings extend the period of sensitivity of the brain to thyroid hormones well into the early phases of gestation when the supply of these hormones is entirely of maternal origin.

Similarly, in human subjects T_4 is already found in the first-trimester coelomic fluid from the 6th week of gestational age, long before the onset of fetal thyroid function which occurs at the 24th week of gestation. The number of T_3 receptors and the amount of T_3 bound to the receptors in the whole brain increase about 500-fold between 10 and 18 weeks, also before the onset of fetal thyroid function. At term about 20–50 % of the cord serum T_4 is still of maternal origin (Vulsma, 1998).

These findings emphasize the importance of maternal thyroxinaemia for the availability of thyroid hormones to the developing brain of the fetus. The findings suggest that brain damage in severe I deficiency is much more severe than brain damage due to sporadic congenital hypothyroidism; in the latter condition maternal thyroxinaemia is normal and fetal serum T_4 of maternal origin is able to protect the fetal brain during fetal life. This factor explains why, in sporadic congenital hypothyroidism, early and adequate substitutive therapy with T_4 almost entirely prevents any brain damage in the affected children (Van Vliet, 1998).

https://doi.org/10.1017/S0029665100000094 Published online by Cambridge University Press

In contrast, in severe I deficiency maternal hypothyroidism does occur during pregnancy, and the contribution of maternal T_4 to the saturation of the T_3 receptors in the brain of the growing fetus is decreased, resulting in the development of the neurological features of endemic cretinism.

Additional roles of selenium deficiency and thiocyanate overload

One stimulating new concept in the aetiology of brain damage, mental retardation and endemic cretinism in severe I deficiency is the combined role of I and Se deficiencies, together with thiocyanate overload resulting from a cassava-based diet. Se is present in high concentrations in the normal thyroid. It is present in GSH peroxidase and superoxide dismutase, the enzymes of the thyroid responsible for the detoxification of toxic derivatives of O_2 (H_2O_2 and perhaps O_2). Se is also present in type I iodothyronine 5′-deiodinase which is responsible for the peripheral conversion of T_4 to T_3 (Delange, 1994).

The influence of Se deficiency on thyroid function and brain development in the fetus in the presence of I deficiency can be summarized as follows (Vanderpas *et al*. 1990; Contempré *et al*. 1991): I deficiency results in hyperstimulation of the thyroid by TSH and consequently in the increased production of H_2O_2 within the cells. Se deficiency results in GSH peroxidase deficit and consequently in accumulation of H_2O_2. Excess H_2O_2 could induce thyroid cell destruction and finally thyroid fibrosis, resulting in thyroid failure. On the other hand, deficiency in iodothyronine 5′-deiodinase in pregnant mothers induced by Se deficiency causes decreased catabolism of T_4 to T_3, and thus increased availability of maternal T_4 for the fetus and its brain. Thiocyanate aggravates the effects of I deficiency.

This concept explains why in situations characterized by isolated severe I deficiency, such as in New Guinea (Choufoer *et al*. 1965; Pharoah *et al*. 1984), China, Indonesia (Boyages & Halpern, 1993) and Thailand (Rajatanavin *et al*. 1997), the clinical picture of endemic cretinism is characterized by a dominant neurological picture, and why, when Se deficiency and thiocyanate overload are added, as in RDC, the neurological signs are mitigated and the picture is dominated by severe hypothyroidism.

Finally, all these abnormalities can be prevented when a normal I supply is provided to the mother before pregnancy.

In conclusion, it has now been clearly demonstrated that the main impact of I deficiency on human subjects is much more on the brain than on the thyroid. Ongoing Universal Salt Iodization programmes, massively implemented around the world by UNICEF and WHO with the support of ICCIDD, aim at the sustainable elimination of I deficiency as a cause of brain damage.

References

Aghini-Lombardi F, Pinchera A, Antonangeli L, Rago T, Chiovato L, Bargagna S, Bertucelli B, Ferretti G, Sbrana B, Marcheschi M & Vitti P (1995) Mild iodine deficiency during fetal/neonatal life and neuropsychological impairment in Tuscany. *Journal of Endocrinological Investigation* **18**, 57–62.

Bernal J & Nunez J (1995) Thyroid hormones and brain development. *European Journal of Endocrinology* **133**, 390–398.

Bleichrodt N & Born MP (1994) A metaanalysis of research on iodine and its relationship to cognitive development. In *The Damaged Brain of Iodine Deficiency*, pp. 195–200 [JB Stanbury, editor]. New York: Cognizant Communication.

Boyages SC & Halpern JP (1993) Endemic cretinism: toward a unifying hypothesis. *Thyroid* **3**, 59–69.

Burrow GN (1972) *The Thyroid Gland in Pregnancy*. Philadelphia, PA: Saunders.

Choufoer JC, Van Rhijn M & Querido A (1965) Endemic goiter in Western New Guinea. II. Clinical picture, incidence and pathogenesis of endemic cretinism. *Journal of Clinical Endocrinology and Metabolism* **25**, 385–402.

Contempré B, Dumont JE, Bebe N, Thilly CH, Diplock AT & Vanderpas J (1991) Effect of selenium supplementation in hypothyroid subjects of an iodine and selenium deficient area: the possible danger of indiscriminate supplementation of iodine deficient subjects with selenium. *Journal of Clinical Endocrinology and Metabolism* **73**, 213–215.

Delange F (1994) The disorders induced by iodine deficiency. *Thyroid* **4**, 107–128.

Delange F (1998) Screening for congenital hypothyroidism used as an indicator of IDD control. *Thyroid* **8**, 1185–1192.

Delange F (2000) Endemic cretinism. In *The Thyroid. A Fundamental and Clinical Text*, 8th ed. [LE Braverman and RD Utiger, editors]. Philadelphia, PA: Lippincott. (In the Press).

Delange F, Bourdoux P, Ketelbant-Balasse P, Van Humskerken A, Glinoer D & Ermans AM (1983) Transient primary hypothyroidism in the newborn. In *Congenital Hypothyroidism*, pp. 275–301 [JH Dussault and P Walker, editors]. New York: M. Dekker.

Delange F, Bourdoux P, Laurence M, Peneva L, Walfish P & Willgerodt H (1993) Neonatal thyroid function in iodine deficiency. In *Iodine Deficiency in Europe. A Continuing Concern*, pp. 199–210 [F Delange, JT Dunn and D Glinoer, editors]. New York: Plenum Press.

Delange F, Iteke FB & Ermans AM (1982) *Nutritional Factors Involved in the Goitrogenic Action of Cassava*. Ottawa, Ont.: International Development Research Centre.

De Long G, Robbins J & Condliffe PG (1989) *Iodine and the Brain*. New York: Plenum Press.

Fierro-Benitez R, Ramirez I, Estrella E & Stanbury JB (1974) The role of iodine deficiency in intellectual development in an area of endemic goiter. In *Endemic Goiter and Cretinism: Continuing Threats to World Health Pan American Health Organization Publication* no. 292, pp. 135–142 [J Dunn and GA Medeiros-Neto, editors]. Washington, DC: Pan American Health Organization.

Fisher DA & Klein AH (1981) Thyroid development and disorders of thyroid function in the newborn. *New England Journal of Medicine* **304**, 702–712.

Glinoer D (1997*a*) The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocrine Reviews* **18**, 404–433.

Glinoer D (1997*b*) Maternal and fetal impact of chronic iodine deficiency. *Clinical Obstetrics and Gynecology* **40**, 102–116.

Glinoer D, De Nayer P, Delange F, Toppet V, Spehl M, Grun JP, Kinthaert J & Lejeune B (1995) A randomized trial for the treatment of excessive thyroid stimulation in pregnancy: maternal and neonatal effects. *Journal of Clinical Endocrinology and Metabolism* **80**, 258–269.

Hetzel BS (1983) Iodine deficiency disorders (IDD) and their eradication. *Lancet* **ii**, 1126–1129.

https://doi.org/10.1017/S0029665100000094 Published online by Cambridge University Press

Morreale de Escobar G, Obregon MJ, Calvo R, Pedraza P & Escobar del Rey F (1997) Iodine deficiency, the hidden scourge: the rat model of human neurological cretinism. In *Neuroendocrinology*, pp. 55–70 [CH Hendrich, editor]. Trivandrum, India: Research/Signpost.

Obregon MJ, Calvo RM, Escobar del Rey F & Morreale de Escobar G (1998) Thyroid hormones and fetal development. In *The Thyroid and Age*, pp. 49–73 [A Pinchera, K Mann and U Hostalek, editors]. Stuttgart: Schattauer.

Pharoah POD, Connolly KJ, Ekins RP & Harding AG (1984) Maternal thyroid hormone levels in pregnancy and the subsequent cognitive and motor performance of the children. *Clinical Endocrinology* **21**, 265–270.

Rajatanavin R, Chailurkit L, Winichakoon P, Mahachoklertwattana P, Soranasataporn S, Wacharasin R, Chaisongkram V, Amatyakul P & Wanarata L (1997) Endemic cretinism in Thailand: a multidisciplinary survey. *European Journal of Endocrinology* **137**, 349–355.

Stanbury JB (1994) *The Damaged Brain of Iodine Deficiency*. New York: Cognizant Communication.

Stanbury JB, Delange F, Dunn JT & Pandav CS (1998) *Iodine in Pregnancy*. New Delhi: Oxford University Press.

Thilly CH, Delange F, Lagasse R, Bourdoux P, Ramioul L, Berquist H & Ermans AM (1978) Fetal hypothyroidism and maternal thyroid status in severe endemic goiter. *Journal of Clinical Endocrinology and Metabolism* **47**, 354–360.

Vanderpas JB, Contempré B, Duale NL, Goossens W, Bebe N, Thorpe R, Ntambue K, Dumont J, Thilly CH & Diplock AT (1990) Iodine and selenium deficiency associated with cretinism in Northern Zaire. *American Journal of Clinical Nutrition* **52**, 1087–1093.

Van Vliet G (1998) Treatment and outcome of neonatal hypothyroidism. In *The Thyroid and Age*, pp. 109–120 [A Pinchera, K Mann and U Hostalek, editors], Stuttgart: Schattauer.

Vermiglio F, Lo Presti VP, Scaffidi Argentina G, Finocchiaro MO, 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. *Clinical Endocrinology* **42**, 409–415.

Vulsma T (1998) Transplacental transfer of thyroid hormones. In *The Thyroid and Age*, pp. 39–48 [A Pinchera, K Mann and U Hostalek, editors]. Stuttgart: Schattauer.

World Health Organization (1996) Iodine. *Trace Elements in Human Nutrition and Health*, pp. 49–71. Geneva: WHO.

World Health Organization/United Nations for Children's Fund/International Council for Control of Iodine Deficiency Disorders (1994) *Indicators for Assessing Iodine Deficiency Disorders and their Control Through Salt Iodization. WHO/NUT/94.6*. Geneva: WHO.

https://doi.org/10.1017/S0029665100000094 Published online by Cambridge University Press