

Review Article

Congenital Hypothyroidism: A Variety of Clinical and Mental Signs

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Abstract

Background: Congenital Hypothyroidism (CH) is defined as a deficiency of the production of the thyroid hormones at birth. The main factors that cause CH is first of all the abnormal development of the thyroid gland and secondly the disorder of the thyroid hormones at the time of biosynthesis. Nowadays the neonatal screening provides us with the opportunity to have a prompt and valid diagnosis protecting the health of the foetus from the side effects of CH. In Cyprus data from an epidemiologic study show that in the decade between 1990 and 2000 the frequency of the disease comes up to 1:1800 children.

Objective: The objective of this review is to look into the variety of clinical and mental signs that people with CH manifest.

Methodology: A complex research was conducted by the international and Greek bibliography from the databases Pubmed, Google Scholar and Scopus. The articles from the year 2005 onwards were studied.

Results: The variety of clinical and mental signs of people with CH from the age of 2 to 26 years old were studied in the context of 10 relevant studies from all over the world. The spectre of clinical signs that is studied includes anatomic abnormalities, mobility problems, obesity problems, low fertility in women, partial deafness, vision problems and finally abnormalities in the urine system and kidneys. The spectre of the mental abilities is characterized by a poor quality of life, low self-esteem and a retarded socialisation. Finally, a special reference was made to the IQ due to the fact that the IQ is a major factor that can possibly affect both the mental and the clinical signs.

Conclusions: It is evident that CH is a disease that can affect its patients with many ways and make their life harder.

Key Words: congenital hypothyroidism, neonatal screening, risk factors

Introduction

Congenital Hypothyroidism (CH) is defined as a deficiency of the production of the thyroid hormones at birth. This deficiency is more often caused due to a problem that appears during the development of the thyroid gland (dysgenesis) or a disorder in the biosynthesis of the thyroid hormones (dysmorphogenesis) (Rastogi & LaFranchi, 2010). The main reason for the appearance of CH due to the impaired biosynthesis of the thyroid hormones is the iodine deficiency. The iodine deficiency occurs to populations living in areas where the soil has a low iodine content. Crops grown in this soil, therefore, do not provide adequate amounts of iodine when consumed (WHO, 2014). As far as dysgenesis is concerned, the vast majority of cases are due to the defects in thyroid differentiation, migration, or growth resulting in athyreosis, ectopy, or in situ hypoplastic glands. It has to be noted that a great number of cases with ectopy or athyreosis remain unexplained. Also, most single gene disorders have been found in patients with in situ glands (Deladoëy et al, 2007).

Studies from the bibliography verify that risk factors for the appearance of CH are the birth of twins, birth defects, female gender, gestational age >40 weeks, family history of thyroid diseases among parents, maternal diabetes, intrauterine growth retardation, preterm delivery and parental consanguinity. It has to be noted that that parental consanguinity appears more often in countries like Iran, where the laws allow the marriage of relatives (Medda et al, 2005; Hashemipour et al, 2007).

In most cases CH, the problem cannot be prevented. However, there are certain measures that can be taken on the part of the mother during pregnancy that can reduce the risk. Primarily, mothers shouldn't be under therapy with radioactive iodine or to use iodine as antiseptic and also they should intake sufficient but not an overdose of iodine (Rastogi & LaFranchi, 2010).

More specifically:

- The improvement of women's habits during fertility age making sure that they intake sufficient vitamins through food and inorganic elements and especially folic acid

and iodine and it is also recommend that they should avoid drinking alcohol.

- They should monitor pregnancy diabetes by keeping under control their weight, their diet and insulin should be administered if it is necessary.
- They should avoid being exposed to harmful substances of the environment such as heavy metals, insecticides and certain medicines during pregnancy
- They should be immunized especially against the virus of rubella for the women and children. This can be prevented with child immunization. The rubella vaccine can also be administered to women without immunization one month before pregnancy at least (WHO, 2014).

Incidence of CH

An increased global incidence (all etiologies included) of CH has been reported from the United States over the past two decades. It is suggested that the increase in reported diagnoses likely reflects more benign and transient cases of CH being identified. Demographic factors such as the change in the composition of different ethnic groups and the increased number of low-birth weight babies are factors that could account in the United States. Also, increased incidence may in part reflect in screening methods. From these facts, it become obvious that the incidence of CH is greatly affected by the geographical region of the planet and in some cases the increase is art factual and in some other cases the increase is real due to the effect of environmental factors (Deladoëy et al, 2011).

In Greece, during those 11 years from the relevant reference to the Cyprian population, 61 cases of permanent CH were diagnosed. The diagnosis of the temporary CH was conducted on 25 patients. Based on a total number of analysed samples, the frequency of the CH is estimated to be 1:1800 with gender percentage of female/male 2.05:1. This difference is significantly higher than the expected 1:3.000 which is observed in most countries. Based on analysis of division Poisson with a rate of mid-p 0.00014 that ends up in a rate of p 0.00029, that shows the number of children with CH is significant different from the number of children with CH in other

countries with a 1% level of significance (Skordis et al, 2005).

In Europe a summary of the European program that was conducted during the period 2000-2003 in New York, indicated some very interesting demographic changes concerning the frequency of CH. Compared to the total frequency of CH, the frequency of the appearance of the disease was somehow lower among the White population (1:1815) and the Black one (1:1902) and it was relatively higher in the Hispanic population (1:1559). Moreover, in New York they found out that the frequency was almost doubled in the births of twins (1:876) compared to the births of single babies (1:1765) and the duration was even higher in the cases of multiple births (1:575). Also mothers of an older age (>39 years old) had a higher frequency (1:1.328) compared to the younger ones (< 20 years old, 1:1.703). The disease appeared more frequently and at a higher rate in premature babies, but it was not evident whether CH in premature babies was temporary or permanent (Rastogi & LaFranchi, 2010).

Denmark is one of the few countries that a triple check-up about CH is applied on newborn babies measuring at the same time the levels of T4, TSH and thyroglobulin. From April 2002 to 2004, 430.764 newborn babies were given a check-up. Out of 772 newborns with pathological results, 29% was diagnosed with CH with the frequency of permanent primary CH to be estimated at 1:2500 births. The results for permanent central CH was estimated at a rate of 1:21.000, whereas of the temporary hypothyroidism was 1:12.000 births. 71% of the children with pathological results did not develop CH and the false positive results of 50% of the cases were due to the deficiency of thyroglobulin. The remaining 50% developed serious problems during the screening process. Despite the fact that there had been a repetitive screening process, 13 children were not diagnosed with the disease. This had as a result to raise the rate of CH to 1:1800 births (Kempers et al, 2006).

A recent study showed that the implication in USA rose from 1:4.094 in the year 1987 to 1:2.372 in the year 2005. The reasons for this increase were not specified, but a possible

explanation might bring around some changes in the tests. Moreover, there is a change of frequency among various racial and ethnic groups since the combination of these groups has changed as well. Many programs of the USA have reported a higher frequency at the populations of Asia, America and Spain, whereas lower frequency was observed in black Americans compared to the white ones (Rastogi & LaFranchi, 2010).

Screening of CH

The most basic and the most widely method that is applied by all screening programs by almost every given country in order to detect CH, is by having a blood test with blood taken from the heel. The blood is collected in a special filtering paper, when the baby is between the fourth and the seventh day after birth. Some programs instead of taking a blood sample from the heel, they use a blood sample taken from umbilical cord. Several countries, such as Japan, Australia, and most European countries, have a TSH-based screening program, whereas many states in North America have a T4-based screening program with additional measurement of TSH in the samples with the lowest T4 concentration. The Dutch prefer to use a three phase screening method of measuring T4, TSH, TBG (Kempers et al, 2006; Manglik et al, 2005). In case that a newborn has a low or a very low birth weight, a second measurement of TSH must be conducted 4 weeks after its birth (Tylek-Lemańska et al, 2005). The genetic screening is also a method of detecting CH (Narumi et al, 2010). Finally, given the dependence between the developing neonatal brain and the thyroid hormones, treatment must start promptly. It has to be noted that overtreatment may have the exact opposite results and instead of treatment, it can cause further damage (Schokking-Bongers et al, 2013).

The objective of this specific review is to bring to the surface the problems that the sufferers of this disease have to face from the age of 2 to 26 from CH at all the levels of life. Also, the review examines the way that CH can influence their daily routine.

Methodology

A detailed research was carried out taking advantage of the international and Greek

bibliography from the databases Pubmed, Google Scholar and Scopus. We studied the articles from the year 2005 up to date. The articles referred to reviews, clinical and epidemiological studies relevant to our topic. The key words that were used were the following: congenital hypothyroidism, neonatal screening, risk factors and combinations of them. We studied articles that were written both in the Greek and English language. We didn't take into consideration studies of old aged people. We also didn't take into consideration studies that could not clearly distinguish the differences between the bearers of the disease and the healthy ones, referring both to physical and mental aspects.

At first, we came up with 1016 articles. We decided not to include 820 articles, because of the lack of a full text. We also decided not to include 72 articles, because they exceeded a ten year period. From the remaining 118 articles, 22 were excluded, because they were written in some other language. Finally, 10 were chosen relevant to our topic which were later used for our review (figure 1, table 1).

We were confronted with an understandable difficulty trying to distinguish the kind of methodologies that were used in this review. This is evident mainly by the tools that were used in order to record the data for our study. These tools in some occasions were quite different to a great extent. Despite all these difficulties, we were able to record the above mentioned data, because the variety of signs of CH is bibliographically verified. We have to admit that not all studies explored the data in the same way, because all the bits of information that were available at the very start were not very relevant between themselves.

Basic elements to be taken into account:

- The sample of the study should include children-youngsters aged 2-26.
- The differences between healthy and sick people at both physical and mental level should be presented distinctly.

Results

Wheeler et al, studied on the one hand up to what extent children and teenagers with CH might have a smaller in size hippocampus and an

abnormal growth compared to their peers and on the other hand this smaller in size hippocampus to be an early indication of a weak memory. The study was conducted in the year 2011 and 35 individuals with CH participated and in control team were 44 individuals. All the individuals belonged to the age group between 9-15. They were evaluated by using standardized IQ tests as well as verbal and visual memory tests and finally magnetic resonance imaging (MRI) was applied. Parents had to fill out a questionnaire concerning the function of their everyday memory. The size of the right and left hippocampus were measured by hand. The results showed that the participants with CH had a significant lower score ($P < 0,001$) compared to the control team at the IQ test. The result was not of course considered as a relevant covariate, because it is an integral part of CH profile. It has also to be noted that the individuals with CH had significantly worse scores compared to the control team in most memory tests. In addition, in the questionnaire that was filled out by the parents, it became apparent that the team with CH had more memory problems in relation to the control team. Finally, the team with CH had a significantly smaller size of hippocampus in relation to the control team. There wasn't a significant difference in the size of the right hippocampus. It has to be mentioned that the left hippocampus were smaller than the right ones in both teams (Wheeler et al, 2011).

Veer et al, studied the quality of life (QoL) in relation to the health, developmental milestones also called course of life (CoL), sociodemographical outcomes and self-esteem of CH patients with the general population and 2) explore whether the severity of CH was related to these outcomes. The study was carried out in 2007 and 69 adults with CH that were born in Holland between the period 1981-1982. The participants were divided into three teams depending on the severity of their condition. They were asked to fill out a questionnaire "TNO-AZL Questionnaire for Adult's Health related Quality of Life", a questionnaire related to CoL and a questionnaire related to their self-esteem. The results of the study showed that patients with CH had a significantly worse score in most scales of the questionnaire that had to do with CoL in relation to the healthy Dutch. That

was an indication that they run a high risk of having a much lower quality of life. It was also observed that individuals with CH had a much lower self-esteem compared to the general population. Finally, it was found out that it took these individuals much more time as to become integral parts of society (Veer et al, 2007).

Najmi et al, studied the IQ of children with CH through diagnostic and therapeutic variables. The study took place in Isfahan and having in mind the high prevalence of the disease in this specific area, the IQ of children with CH and the influence of the diagnostic and therapeutic variables were explored during this control program for CH. In total in this comparative study, the IQ of 120 children was tested and these children were further divided into three subgroups. The first subgroup dealt with the verbal IQ, the second was the performance IQ and the third was the full scale IQ. Children being diagnosed with temporary congenital hypothyroidism (TCH) and permanent congenital hypothyroidism (PCH) that was measured by using the revised pre-school Wechsler and primary scale of intelligence and they were compared with the control group. The relationship between the IQ score at the beginning of the therapy and the level of TSH was evaluated in the groups under study. The results showed that the average score of the verbal IQ, the performance IQ and the full scale IQ were significantly higher in the control team as opposed to the equivalent average score of the patients diagnosed with temporary and permanent CH. In patients with PCH, despite the fact that it was not significant, there was a rather negative relationship between all types of IQ, the control of TSH and the time of the start of therapy. As far as the patients with TCH are concerned, there had been a negative and significant relationship between the verbal IQ ($r = -0.40$), full scale IQ ($r = -0.38$) and the timing of the start of the therapy ($r = -0.46$). Therefore, the average IQ score of the patients was lower than that of the control group which is related negatively to the timing of the start of the therapy. Thus, despite the fact the check-up for CH and the timely therapy have enhanced the prognosis of the patients, the timely and high dose of therapy in children with CH is recommend (Najmi et al, 2013).

Arenz et al, carried out a study having as an objective the evaluation of the mental score, mobility skill and the BMI in children with CH. For this specific study 18 children aged between 4.9 to 5.8 with permanent CH were chosen and which were born in 1999 in Bayern. The evaluation was carried out at the residence of the children or at the building of the local health centre with the written consent of the parents, whereas the protocol of the study was approved by the Ideology Committee of the Medical Association of Bayern. Once a therapy with levothyroxine was administered and which started after approximately 7.2 days (range 4-15) with an average dose 12.0 $\mu\text{g}/\text{kg}$ (range 7.2-17.0), the IQ of the children was measured at 100.4. No child had an IQ score lower than the normal. As far as the reaction and the mobility speed are concerned, were considerably lower in children with CH. Children with an initial rate of TSH greater than 200 mU/L presented a worse reaction and mobility speed than the children with a rate of TSH lower than 200 mU/L . There were no differences between the two sexes and there was no proof of any kind of relationship between overweight or obesity and mobility skills.

The average of BMI of children was 16.0 kg/m^2 (range 16.2 – 30.4) and 5 children could be classified as overweight including obesity, whereas 2 of them were obese. If we were to compare the data of the children of Bayern of the same age span, children with CH had a greater risk to be overweight or obese. Finally the results of these study showed that they had an increased prevalence and they run a risk of being overweight compared to the data of the normal ones. They also had partially mobility problems whereas the mental development was normal (Arenz et al, 2008).

Kempers et al, carried out a study in 2006 in order to examine whether the beginning of the therapy within 20 days contributed to having enhanced cognitive and mobility outcome. The patients that took part were 82 Dutch with thyroidal CH (CH-T) born in the years 1992 and 1993 and they were treated in 20 days taken into consideration their cognitive and mobility outcome (average age 10.5 years, range 9,6-11.4 years).

Figure 1. Study selection chart

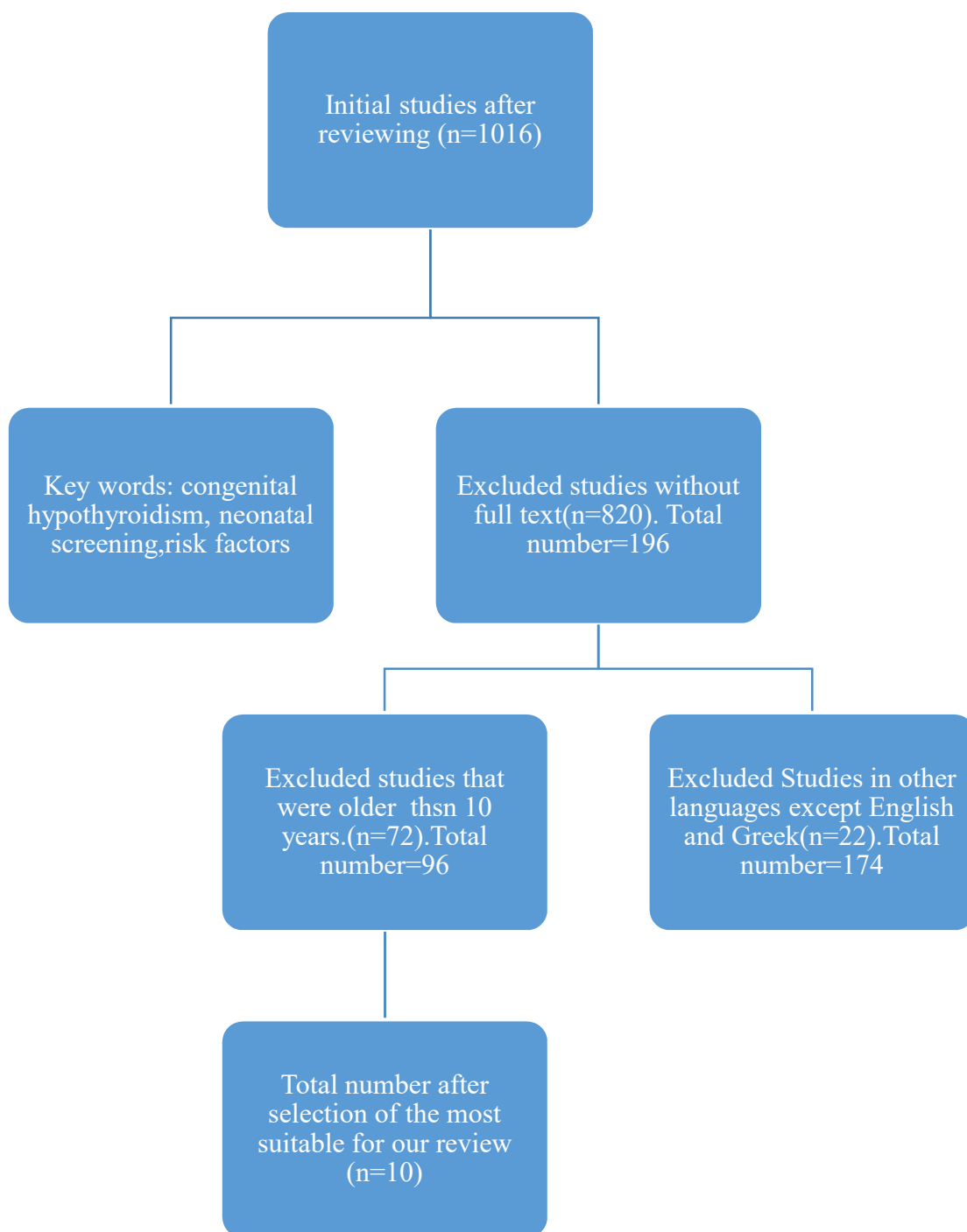


Table 1. Comprehensive outline of the studies included in the present paper

No	Author(s)	Title	Country	n	Age/yrs	Methods	Statistical analysis/p value
1.	Wheeler SM et al(2011)	Hippocampal Size and Memory Functioning in Children and Adolescents with Congenital Hypothyroidism	Canada	79	8.7–14.9	MRI techniques	SPSS version 17/ p<0.1
2.	Veer LS et al(2007)	Quality of Life, Developmental Milestones, and Self-Esteem of Young Adults with Congenital Hypothyroidism Diagnosed by Neonatal Screening	Holland	69	Mean 21.5	Questionnaire	SPSS version 12.0- p<0.01
3.	Najmi SB et al(2013)	Intelligence quotient in children with congenital hypothyroidism: The effect of diagnostic and treatment variables	Iran	120	4-6	Questionnaire	SPSS- p<0.03
4.	Arenz S et al(2008)	Intellectual outcome, motor skills and BMI of children with congenital hypothyroidism: a population-based study	Germany	21	4.9-5.8	Questionnaire	SUDAAN SAS

The severity of CH-T was classified according to pre-treatment of free T4 concentration. The results were analysed in relation to the cause and the severity of CH and in relation again to the variables of the therapy. Patients with severe CH-T had lower full-scale (93.7), verbal (94.9), and performance (93.9) IQ scores than the normal population ($P < 0.05$), whereas IQ scores of patients with moderate and mild CH-T were comparable to those of the normal population. In all three severity subgroups, significant mobility problems were observed, most pronounced in the severe CH-T group. No correlations were found between the starting day of treatment and IQ or mobility outcome (Kempers et al, 2006).

Hassani et al, carried out a study to evaluate the fertility with CH that had been treated at the first stages and its determinants. The study took place in December 2011 in France. In total 1748 individuals were diagnosed with CH the first 10 years since the introduction of the neonatal screening in France, whereas 1158 individuals filled out a questionnaire in relation to fertility

with an average age 25,3 years. This self-administered questionnaire focused on the first attempts to have a child as well as the duration on pregnancy. The control group was used in a similar study on individuals born in the years between 1971 and 1985. These individuals had a normal birth weight. 4 out of 886 had a normal weight at birth taken into consideration the duration of the pregnancy and they were monitored up to the age of 30 at which they had died. However, there was no contact with 88 and 79 refused to participate in the study. Therefore, 715 control individuals were included in the study. The fertility ability was similar for the CH and control groups: HR = 1.14 (0.89–1.47) for women, and HR = 0.98 (0.58–1.66) for men. In women, the most severe initial forms of the disease, athyreosis, absence of bone maturation at the knee epiphyseal ossification centers, and a low serum free T4 concentration at diagnosis (<5 pmol/liter), were associated with lower fertility: HR = 0.68 (0.50–0.98) ($P = 0.02$); HR = 0.65 (0.45–0.94) ($p = 0.02$) and HR = 0.70 (0.50–

0.97) ($P = 0.03$), respectively. However, fertility was not associated with age at the start of treatment, initial levothyroxine dose, or the adequacy of hypothyroidism control. Consequently there is no proof that fertility is generally lower at young adults that were treated early as opposed to the general population. However, fertility was lower with women that suffered from the most severe form of the disease (Hassani et al, 2011).

Kempers et al, studied the cognitive and mobility function of young adults with CH that were born 2 years after the introduction of the Dutch neonatal screening program. The study took place in 2005 and 70 patients took part of an average of 21.5. 49 out of them had been screened at an earlier age (9.5 years). CH was characterized as mild, moderate and severe condition based on the concentration of T4 before treatment is administered. The average score of the patients with CH was significantly lower in relation to that of the general population. Also, the total scores of the patients with CH in the mobility tests were again significantly worse in comparison to the score of the control group. Finally, there were significant differences between the three subgroups in which the patients were divided concerning the IQ tests (Kempers et al, 2005).

Bisacchi et al, in a cross-sectional study compared the psychological adjustment and behaviour of congenital hypothyroidism (CH) children and their parents with a control group. In this study 84 children with CH participated and the participants were subdivided into four age groups (2-5, 6-10, 11-13 and 14-18) and they compared with a control group. Patients were evaluated using two different questionnaires: Child Behaviour Checklist for parents and Youth Self-Report for children over 11 years of age. The first questionnaire was filled out by the parents of all children and the second one by children 11 years old and over. The results of the study showed that the participants that belonged to group 1, 3 and 4 did not have any major differences in comparison to the participants of the control group. In spite of this fact group 2 had achieved a much higher score than the control group. That is to say, the higher

scores were indicative of more problems (Bisacchi et al, 2011).

Léger et al, studied and assessed the health status and the socioeconomic attainment of a population-based registry of young adult patients. All 1748 patients that were evaluated, they were diagnosed in the first decade of the introduction of the neonatal screening in France and they were asked to take part in the study. The average age was 23.4 years old. All of them were given questionnaires that were returned filled out by 1202. The comparison group included 5817 participants from the last French survey that was conducted the last ten years. The results indicated that the patients with CH had much greater chances in comparison to their peers to develop in the future chronic diseases, partial hearing impairment, visual and obesity problems. It was also observed that it was more likely for them to live with their parents and to have a lower quality of life compared to their healthy peers as far as their mental dimensions are concerned. The severity of CH during diagnosis, the efficiency of therapy and the presence of other chronic diseases were the main definitive factors for the educational status of the patients and health-related quality of life scores (Léger et al, 2010).

Kumar et al, investigated the prevalence of congenital renal and urologic anomalies in children with congenital hypothyroidism to determine whether further renal and urologic investigations would be of benefit. The data referring to the prevalence of CH were received from the New York State Congenital Malformation Registry. The likelihood of appearance of urinary tract anomalies were calculated for children with congenital hypothyroidism and compared to children without congenital hypothyroidism. In addition, the researchers obtained further CH data from New York State newborn screening, and the cases were matched to Congenital Malformation Registry. The analysis of data of Congenital Malformation Registry showed 980 children with CH and 3.661.585 without CH. All the children were born in the state of New York between 1992 and 2005. As the study showed, children with CH had increased chances of developing abnormalities in the urinary system and the

kidneys with odds ratio 13.2(10.6-16.5). The other significantly increased defects in congenital hypothyroidism were cardiac, gastrointestinal, and skeletal(Kumar et al, 2009).

Conclusions

As it is well known hypothyroidism is the most common thyroid disease, its frequency affects both sexes. As far as the diagnosis of the CH is concerned, the technique that is most commonly used is the measurement of the TSH levels through blood tests taken from the heel or the umbilical cord of the newborn.

A significant deficiency of TSH for several weeks after the birth of the newborn might cause severe cognitive, mobility and mental abnormalities in the patient. CH is caused mainly by postnatal deficiency of TSH, because during pregnancy the mother provides sufficient quantities of the thyroid hormones to the foetus. Numerous in vitro studies in animals have shown that the malfunctioning of the thyroid gland reduces the neural development and differentiation in the hippocampus, cerebral cortex and cerebellum. As far as the hippocampus is concerned, it is observed in lots of cases that it has been reduced in size having as a result patients with CH facing difficulties to respond and manage their daily routine due to the fact that their memory is weak(WHO,2014).

It is evident that the IQ is a major factor in itself that is affected greatly by CH. As it has been proven by several studies, patients with CH tend to have a lower IQ compared to their peers. It has to be noted that newborns, despite the fact that they were diagnosed with CH and therapy with levothyroxine started right away, 9 days after their birth as a matter of fact, their IQ was much lower after a while. Therefore, it's obvious that there is no immediate correlation between a prompt therapy and a mental improvement of patients with CH(Arenz et al, 2008).

The mobility problems that patients with CH are faced with are a common condition. It has been noted by previous studies that the mobility problems are directly related to the severity of hypothyroidism. That is to say if somebody suffers from a severe form of hypothyroidism then his mobility problems are expected to be greater as well later on in life. It has to be

mentioned that the mobility problems tend to appear early in childhood, making their life much more difficult as they often have balance problems(Kempers et al, 2006; Kempers et al, 2005).

As far as the fertility of CH patients is concerned, generally speaking no great differences have been observed between healthy individuals and patients. The only women that had lower fertility rates were the ones with the most severe form of the disease and that was an indication that hypothyroidism, as it seems, might affect the reproductive organs. It is interesting however to be mentioned that in a recent study that was applied on female mice, it was observed that there was no fertility improvement despite the fact that they had been subjected to substitute therapy. It has also to be noted that the reason that the mice remained infertile was due to the fact that they failed to develop a functional uterus(Hassani et al, 2011).

Apart from the clinical signs of the CH there are also the social ones. It appeared that they neither had a particular problem as far as their sexual life is concerned nor that they were less happy than the healthy ones. Despite all these positive elements, the patients believed that hypothyroidism had a negative impact on their daily life and they also experienced a lower self-esteem. Moreover, these patients were in general more vulnerable to become depressive and at times they expressed antisocial behaviour compared to the healthy population. If we were to take into account that all the above mentioned problems coexisted with some clinical signs, then it is obvious that the sentimental and emotional condition of these people is much easier to be disturbed. Children with CH are most at risk and this is explained because they happen to compare themselves and their achievements with the healthy ones. At last, it has to be mentioned that the children's behavioural problems as well as their emotional disturbances can greatly affect their parent's emotional state as well(Najmi et al, 2013; Bisacchi et al, 2011; Léger et al, 2010).

Thus, if CH is not detected and not promptly treated, then it leads to an irreversible mental retardation. Then, the mass neonatal screening through the detection programs is considered one of the greatest achievements of medicine in the

20th century. Parent's education concerning the disease is the golden key as for the patients to follow their therapy. It is imperative to be comprehended by everybody, because CH is a disease that is expressed in multiple forms concerning the physical, mental and social level.

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