Endocrine and metabolic features of familial longevity : the Leiden Longevity Study

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Chapter 9: Familial longevity is associated with decreased thyroid function

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Abstract

A relation between low thyroid activity and prolonged lifespan in humans has been observed. Several studies have demonstrated hereditary and genetic influences on thyroid function. The aim of this study was to test whether low thyroid activity associated with extreme longevity constitutes a heritable phenotype which could contribute to the familial longevity observed in the Leiden Longevity Study. The Leiden Longevity Study comprises 859 nonagenarian siblings (median age 92.9 year) from 421 long-lived families. Families were recruited from the entire Dutch population if at least two long-lived siblings were alive and fulfilled the age-criterion of 89 years or older for males and 91 years or older for females. There were no selection criteria on health or demographic characteristics. In the present study we calculated the Family Mortality History score of the parents of the nonagenarian siblings and related this to thyroid function parameters in the nonagenarian siblings. We found that a lower family history score (less mortality) of the parents of nonagenarian siblings was associated with higher serum thyrotropin levels ($p=0.005$), lower free serum thyroxine levels ($p=0.002$) as well as lower free triiodothyronine levels ($p=0.034$) in the nonagenarian siblings. Our findings support the previous observation that low thyroid activity in humans constitutes a heritable phenotype which contributes to exceptional familial longevity observed in the Leiden Longevity Study.

Introduction

A relation between low thyroid function and prolonged lifespan in elderly humans has been noted [1, 2]. In the oldest old, higher concentrations of thyrotropin are associated with a survival benefit without detrimental effects on ability or mood. Contrastingly, at old age decreased serum thyrotropin and raised serum free thyroxin levels are related to an increased risk of mortality.[3] Hereditary and genetic influences on thyrotropin and serum thyroid hormone concentrations have been reported in multiple studies. The lower thyroid activity associated with extreme longevity might therefore constitute a heritable phenotype [4-8].

In order to identify heritable determinants of longevity we designed the Leiden Longevity Study. This study comprises nonagenarian siblings, recruited from families based on proband siblings that both exhibit exceptional longevity [9]. We also included the offspring of the nonagenarian siblings, which are enriched for heritable influences on morbidity and mortality [10]. In line with the observed association between low thyroid function and longevity, we showed that the middle-aged offspring of nonagenarian siblings indeed have lower thyroid hormone levels when compared to middle-aged controls [11]. In the nonagenarian siblings however, comparative analysis of the association between low thyroid function and longevity is hampered by their extreme age, which precludes the use of proper age-matched controls.

To examine the relation between low thyroid function and longevity in the nonagenarian siblings we calculated a family history score describing the mortality of the parents of the nonagenarian siblings [12]. We reasoned that in nonagenarian siblings from parents with a lower family history score (i.e. lower than expected mortality), traits related to longevity would be more pronounced than in nonagenarian siblings from parents with a higher family history score. Therefore we hypothesized that lower family history score of the parents of the nonagenarian siblings is related to higher thyrotropin levels and lower serum thyroxine levels in the nonagenarian siblings.

Materials and methods

Leiden Longevity Study

In the Leiden Longevity Study, 421 families were recruited consisting of long-lived Caucasian siblings together with their offspring and the partners thereof. Between 2002 and 2006 families were recruited if at least two long-lived siblings were alive and fulfilled the age-criterion of 89 years or older for males and 91 years or older for females, representing less than 0.5 % of the Dutch population in 2001. There were no selection criteria on health or demographic characteristics. Blood samples were taken at baseline for extraction of DNA, RNA and the determination of non-fasted serum and plasma parameters. Blood samples were obtained

throughout the day between 9:30 a.m and 17:00 p.m Moreover, data on disability, global cognitive function and self perceived health were collected. The Medical Ethical Committee of the Leiden University Medical Centre approved the study and informed consent was obtained from all subjects. Of the 944 nonagenarians of the Leiden Longevity Study, data on thyrotropin, thyroxine and triiodothyronine levels and sampling time were available for 859 of the nonagenarian participants. Of the 421 families included in this study, 344 (81.7%) families contributed 2 nonagenarian siblings, 67 families have contributed 3 nonagenarian siblings (23.3%), 9 families have contributed 4 nonagenarian siblings (4.2%), 1 family has contributed 5 nonagenarian siblings (0.6%).

Chemical analyses

All serum measurements were performed with fully automated equipment. For thyrotropin, free thyroxine and free triiodothyronine, the Modular E170 was used, for high sensitivity C-reactive protein (hsCRP) the Cobas Integra 800 was used, both from Roche, Almere, the Netherlands. The coefficients of variation of these measurements were all below 5 %. All chemical analyses were performed in a single batch at the Department of Clinical Chemistry, Leiden University Medical Center, the Netherlands, excluding the possibility of confounding by batch effects. In our laboratory, the reference values for thyrotropin were 0.3-4.8 mIU/L; free thyroxine: 10-24 pmol/L; and free triiodothyronine, 2.5-5.5 pmol/L. Of the 859 participants, 746 participants (86.8%) were euthyroid; 5 had overt hyperthyroidism (0.6%); 43 (5.0%) had subclinical hyperthyroidism; 7 (0.8%) had overt hypothyroidism; 58 (6.8%) had subclinical hypothyroidism. Additionally, of the 746 euthyroid subjects, 6 subjects had isolated free thyroxine levels outside the reference values and 14 subjects had isolated free triiodothyronine levels outside the reference values. When analyses were restricted to subjects with thyroid function parameters within the reference range 726 subjects were included (that is: 746 euthyroid subjects minus 6 subjects having abnormal levels of thyroxine and 14 subjects having abnormal levels of triiodothyronine).

Disability

In the Leiden Longevity Study disability was determined using the activities of daily living scale (ADL) and Instrumental Activities of Daily Living scale (IADL) [13]. Disability scores in ADLs range from 0 points (fully dependent in all activities) to 20 points (fully independent in all activities). Disability scores in IADLs range from 0 points (fully dependent in all activities) to 14 points (fully independent in all activities). Global cognitive function was assessed with the Mini Mental State Examination (MMSE). Self perceived health was assessed by one question with five alternatives: 1 = “very good”, 2 = “rather good”, 3 = “moderate”, 4 = “rather poor”, 5 = “very poor”. The MMSE scores range from zero points (very severe cognitive impairment) to 30 points

(optimal cognitive function). ADL, IADL, MMSE and self perceived health was available for 779 participants.

Family History Score

Each participating family has provided us with the genealogical information regarding the parents of the nonagenarian siblings, all siblings, and the offspring of the nonagenarian siblings. To reduce possible unreliability of questionnaires and participants' memories, whenever possible, this information was verified by passport, or by birth or marriage certificate. Furthermore, all data were additionally verified with the personal record cards of the deceased family members in the national population registry located at the Central Bureau of Genealogy in The Hague, The Netherlands. For each parent we computed the sex and birth cohort cumulative hazards using the life tables of the Dutch population. A family history score for a family was defined as two minus the sum of the cumulative hazards of the two parents. Note that since both parents are deceased one minus the cumulative hazard equals the martingale residual. The martingale residual is defined as the difference between the event status (0 if alive, 1 if deceased) and the cumulative hazard at the observed age (current age or age at death). The sum of the martingale residuals measures the deviation of survival of the parents with respect to their birth cohort. Therefore negative values mean excess survival and positive values mean excess mortality.

Statistical analyses

The association between family history score and serum thyroid function parameters was assessed using a linear mixed model with a random sibship effect to model correlation of sibling data. Broad heritability of serum thyroid function parameters was estimated with the following formula: heritability = 2 * (between-families variance)/(between-families variance + within-families variance). Distributions of continuous variables were examined for normality and logarithmically transformed when appropriate (thyrotropin and high sensitivity C-reactive protein). The Statistical Package for the Social Sciences (SPSS) program for Windows, version 14.0, was used for data analysis. Graphs were drawn using Graph Pad Prism version 5.

Results

The principal features of the studied population (n=859) are displayed in **table 1**. The median age of the study population was 92.9 years and 38.4% of the study population was male.

First, we examined the broad heritability of serum thyroid function parameters in the cohort of nonagenarian siblings, as shown in **table 2**. To determine to what extent the association between thyroid function and familial longevity was driven by subjects with thyroid function parameters beyond the normal range, we repeated all the analyses in subjects restricted to thyroid function

parameters within the euthyroid range (model 2). Moreover, it has been demonstrated that alterations in thyroid hormone levels can occur during acute or chronic critical illness. This condition, referred to as non-thyroidal illness syndrome is characterized by a variety of alterations in thyroid function parameters that commonly include low serum triiodothyronine along with normal or inappropriately low thyrotropin and serum free thyroxine levels [14]. To exclude the possibility that physical illness played a major role in our findings, particularly regarding triiodothyronine levels, we repeated the analyses after adjustment for ADLs, IADLs and serum high sensitivity C-reactive protein levels. (model 3). Dependent on the used model, heritability of the serum thyrotropin levels varied between 0.41 and 0.49. Heritability of serum levels of free thyroxine and free triiodothyronine ranged from 0.18 – 0.31 and 0.24 – 0.50 respectively.

Table 1. Baseline characteristics of the study population

	Study population
Number participants	859
Males (n, %)	330 (38.4)
Age (year)	92.9 (91.4 – 94.8)
Thyrotropin (0.3 – 4.8 mU/L)	1.51 (0.95 – 2.40)
Free thyroxine (10 – 24 pmol/L)	16.0 (14.4 – 17.6)
Free triiodothyronine (2.5 – 5.5 pmol/L)	4.00 (3.70 – 4.40)
Hyperthyroidism (n, %)	5 (0.6)
Subclinical hyperthyroidism (n, %)	43 (5.0)
Euthyroidism (n, %)	746 (86.8)
Hypothyroidism (n, %)	7 (0.8)
Subclinical hypothyroidism (n, %)	58 (6.8)
High sensitivity C-reactive protein (<10 mg/L)	2.84 (1.28 – 5.95)
Disability (points)	
ADLs	18 (15 – 20)
Instrumental ADLs	8 (4 - 11)
Mini Mental State Examination	26 (22 - 28)
Self perceived health	3 (3 - 4)

Data are presented as median values with interquartile range (25 – 75%). Reference values are given between parentheses.

Table 2. Broad heritability of thyroid function parameters within the study population

	Broad heritability	p-value
Model 1: adjusted for sex and age.		
Thyrotropin	0.41	<0.001
Free thyroxine	0.18	0.049
Free triiodothyronine	0.24	0.009
Model 2: as model 1, restricted to participants with levels within reference values.		
Thyrotropin	0.49	<0.001
Free thyroxine	0.31	0.007
Free triiodothyronine	0.50	<0.001
Model 3: as model 2 adjusted for ADL, IADL, serum hsCRP levels.		
Thyrotropin	0.46	<0.001
Free thyroxine	0.30	0.012
Free triiodothyronine	0.45	<0.001

Next, we assessed the relation between lower family history score of the parents of the nonagenarian siblings and thyroid hormone function parameters in the nonagenarian siblings. For this purpose we calculated the family history score of the parents of the nonagenarian siblings, as depicted in **figure 1**. A family history score of 0 represents the standardized mortality rate of the entire Dutch population. Values below 0 denote excess survival when compared to the Dutch population, while values above 0 denote relative excess mortality. Median family history score was -1.37 (interquartile range: -2.68 - -0.21), indicating that we have recruited families with a higher average survival than the general Dutch population.

Figure 1. Frequency distribution of family history score of the parents of nonagenarian siblings. *A family history score of 0 represents the standardized mortality rate of the entire Dutch population. Values below 0 denote excess survival when compared to the Dutch population, whilst values above 0 denote relative excess mortality.*

Table 3 and **figure 2** show the association between family history score and thyroid function parameters. A lower family history score (lower than expected mortality) was associated with higher serum thyrotropin levels, lower free serum thyroxine levels as well as lower free serum triiodothyronine levels. Similar results were obtained after restriction of analyses to participants with thyroid hormone levels within reference values. We repeated the analyses after adjustment for ADLs, IADLs and serum high sensitivity C-reactive protein levels to exclude possible confounding by physical illness (all p values <0.05).

Table 3 Association between family history score and serum thyroid function parameters

	Change per increase familial mortality history unit	p-value
Model 1: adjusted for sex and age.		
Log thyrotropin (mU/L)	-0.05 (-0.09 - -0.004)	0.032
Free thyroxine (pmol/L)	0.16 (0.05 – 0.26)	0.005
Free triiodothyronine (pmol/L)	0.03 (0.002 – 0.06)	0.034
Model 2: as model 1, restricted to participants with levels within reference values.		
Log thyrotropin (mU/L)	-0.04 (-0.06 - -0.01)	0.005
Free thyroxine (pmol/L)	0.13 (0.04 – 0.23)	0.005
Free triiodothyronine (pmol/L)	0.01 (-0.01 – 0.04)	0.23
Model 3: as model 2 adjusted ADL, IADL, serum hsCRP levels..		
Log thyrotropin (mU/L)	-0.04 (-0.06 - -0.01)	0.005
Free thyroxine (pmol/L)	0.15 (0.05 – 0.25)	0.002
Free triiodothyronine (pmol/L)	0.02 (0.002 – 0.05)	0.034

Data are presented as mean change per unit increase in familial mortality history and 95% confidence intervals.

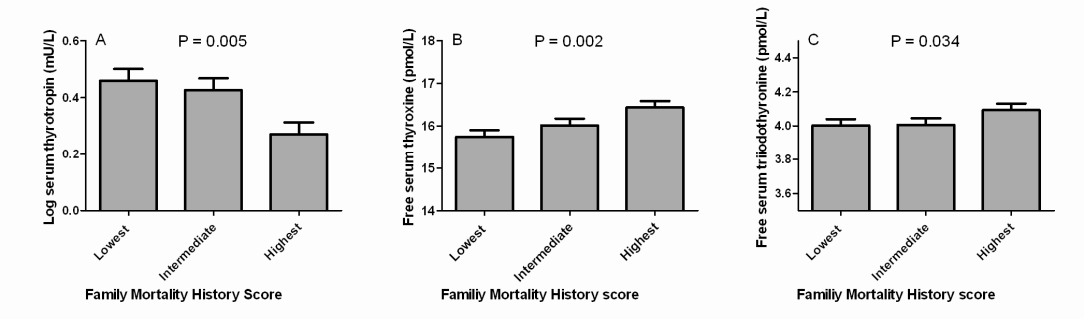

Figure 2A-C. Association between family history score and serum thyroid hormone parameters. *For thyrotropin (A), free thyroxine (B) and free triiodothyronine (C). Bars represent tertiles of family history score scores adjusted for age, sex, ADLs, IADLS, and log serum high sensitivity C-reactive protein. Results were restricted to participants with serum thyroid hormone parameters within reference values.*

Discussion

We aimed to examine the association between lower thyroid function and longevity in our cohort of nonagenarian siblings. We found that a lower family history score (less mortality) of the parents of nonagenarian siblings was associated with higher serum thyrotropin levels, lower free serum thyroxine levels as well as lower free triiodothyronine levels in the nonagenarian siblings. This observation was not explained by differences in physical disability.

Our findings are an important extension of our previous observation of lower free thyroxine levels and lower free triiodothyronine levels along with a tendency towards higher serum free thyrotropin levels in the middle-aged offspring of nonagenarian siblings when compared to controls [11]. Our results not only concur with the reported association between low thyroid hormone function and human longevity[1] , but also support the recently reported observation of low thyroid function as a heritable phenotype contributing to exceptional longevity [2,15]. Moreover, our results are in agreement with earlier studies showing a strong heritability of thyroid function [6-8].

The relation between lower family history score of the parents of the nonagenarian siblings and higher thyrotropin along with lower serum thyroxine levels in the nonagenarian siblings may indicate that lower activity of the thyroid hormone axis is a heritable phenotype which contributes to exceptional longevity. Lower activity of the thyroid hormone axis possibly serves as a mechanism to shift energy expenditure from growth and proliferation to protective maintenance. The phenotype of low thyroid hormone levels observed in our long-lived cohort is reminiscent of the phenotype of murine pituitary mutants with delayed aging, as for example the long-lived Ames and Snell dwarf mice [16, 17]. These model organisms show traits that are hypothesized to be related to thyroid hormone deficiency, and supplementation of thyroid hormone during adulthood partly diminishes their enhanced lifespan.[18] However, unlike our cohort of nonagenarian siblings in which downregulation of the thyroid axis is due to a lower thyroid activity, in these model organisms thyroid hormone deficiency is due to central hypothyroidism at the level of the pituitary.

There are some limitations to our study. First, data on current medication use were not available for the nonagenarian siblings. Furthermore, we have no records of previous history of thyroidal disease, the prevalence of which increases with age. Therefore we could not determine to what extent our observations were affected by thyroid disease and/or its treatment. Thirdly, data on specific SNPs in the thyrotropin receptor which were shown to be associated with higher thyrotropin levels [15], were not available for our cohort. Future research will therefore focus on

unraveling the underlying genetic determinants. Another limitation is that samples were not all drawn fasted at 9:00 a.m. However, additional adjustment for time of blood sampling did not materially change any of the obtained results.

In conclusion our results support the previous observation that low thyroid activity in humans constitutes a heritable phenotype which contributes to exceptional longevity.

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