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ORIGINAL ARTICLE

Undiagnosed silent coeliac disease: A risk for underachievement?

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Abstract

Objective. Silent coeliac disease is reported in 1% of Caucasian populations, but there is a lack of knowledge of its natural course and the risk of complications. The need for population screening is debated. We sought for complications of untreated coeliac disease in a well-defined cohort of Finnish adults. ***Material and methods***. Subjects ($n=2427$, ages 24–39 years) attending the 21-year follow-up visit of the study "Cardiovascular Risk in Young Finns" completed an extensive questionnaire on their health, diet, social situation and family life, and were given a medical examination. Measurement of serum IgA-transglutaminase and IgA-endomysium antibodies identified 21 subjects with silent coeliac disease. ***Results***. The subjects with silent coeliac disease did not differ from the rest of the cohort in age, gender, stature, weight, medical diagnoses (autoimmune, malignant), health concerns, use of alternative medications, physical activity, or in the cause of death their parents. They had lower serum HDL-cholesterol (1.12 versus 1.29 mmol/L; $p=0.015$), as described for active coeliac disease. Fewer (5.3% versus 22.8%; $p=0.047$) had a university or college degree or worked in managerial or professional positions (28% versus 45%; $p=0.112$). ***Conclusions***. The underachievement in education and working life observed in subjects with silent coeliac disease is a new and intriguing finding and may be related to the increased prevalence of depressive and disruptive behavioural disorders described in teenagers with untreated coeliac disease. Our findings add a new ingredient to the ongoing discussion regarding the need for population screening for silent coeliac disease.

Key Words: *Coeliac disease, screening, underachievement*

Introduction

Coeliac disease (CD) is an immunologically mediated injury of the small intestine precipitated by gluten ingestion in genetically susceptible individuals. The classical symptom spectrum includes diarrhoea, abdominal complaints and malabsorption, and the prevalence of symptomatic CD is reported to vary from 1:400 to 1:200 [1–3].

A substantial proportion of patients seek medical advice because of minor or "atypical" symptoms such as fatigue [4], infertility [5], aphthae, anaemia and arthritis [6]. Recently, in children and adolescents with untreated symptomatic CD, we found a significant increase in disruptive behavioural and depressive disorders [7] which respond to a gluten-free diet [8]. Complications of long-standing untreated CD include osteoporosis, autoimmune disorders [9] and gastrointestinal malignancies, mainly small bowel T-cell lymphoma [10,11]. Treatment with a life-long gluten-free diet alleviates symptoms and prevents complications [10,11].

The new sensitive and specific serological tests, such as endomysium [12] and transglutaminase [13] antibody assays enabling screening for silent CD (sCD) in large populations, have now universally shown that undiagnosed sCD is considerably more common than CD diagnosed because of symptoms [14–17], with prevalence figures ranging from 1:200 to 1:80. As yet, there are few data on the natural course and complication risk of these subjects with sCD. They have been described as suffering from various abdominal complaints, iron deficiency and anaemia [17,18], osteopenia [19] and lowered qual-

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ity of life [20]. A significant growth delay independent of gastrointestinal symptoms was observed in 54 seven-year-old children with sCD [21]. The subjective health and use of medical services is reportedly comparable to the general population [18], and their cardiovascular risk profile is low [17]. The excess mortality associated with CD is observed only in the symptomatic patients, not in patients with minor symptoms or detected through screening [22]. The social class of sCD subjects as judged by the highest occupation of the subject or his/her spouse was reportedly not different from the controls [17].

At present, opinion is divided over the need for population screening for sCD. The enthusiasm for mass screening programmes [19,22,23] has waned to some extent, with cautious voices advising that more needs to be known about the natural history of sCD [10,24,25]. A calculation of the cost–benefit ratio of mass screening for CD to prevent long-term complications (osteoporosis, infertility, miscarriage, low birthweight and non-Hodgkin lymphoma) did not support such programmes [26]. Enthusiasm for screening programmes has also been dampened by the observation that compliance with a gluten-free diet is poorer for screening-detected CD subjects than symptomatic CD patients [27], and the finding that diagnosed and treated CD patients experience disease burden [28].

We set out to study the occurrence of sCD and to search for the recognized complications and other possible impacts on life of untreated CD in a large cohort of young adults being followed for coronary heart disease risk factors for 21 years.

Material and methods

Subjects

The study population consisted of a nationally representative cohort of randomly selected Finnish adults (aged 24–39 years) participating since 1980 in the study "Cardiovascular Risk in Young Finns" [29,30]. Of the 3596 subjects originally in the cohort, 2427 (67.5%) took part in the 21-year follow-up visit. This study is being carried out in five university hospitals, with the approval of local ethics committees.

Methods

The subjects and their spouses completed an 86-item questionnaire on their health, dietary habits, social situation and family life. Reported medical diagnoses were grouped by trained personnel according to the national disease classification of 1976, as has been done throughout the 21-year follow-up. The respondents' occupation (kind of work performed and skill required) was classified according to Handbook 14 [31] and socio-economic status according to Handbook 17 [32] of Statistics Finland, formerly Central Statistical Office of Finland. Finland's national Classification of Occupations 2001 is based on the International Labor Organization (ILO) classification of occupations ISCO-88 and Classification of Socioeconomic Groups 1989 is based on the statistical recommendations issued by the UN for the 1990 Population Censuses.

Most of the subjects (2142) submitted to a medical examination with measurements of height, weight and blood pressure and gave a blood sample for the analysis of serum lipids, c-reactive protein and blood glucose. Serum cholesterol, triglyceride and glucose concentrations were measured enzymatically (Olympus Diagnostica GmbH, Hamburg, Germany). HDL cholesterol was determined with the dextrane sulphate 500 000 method [33] and LDL cholesterol concentration was calculated with the use of the Friedewald formula [34]. Serum apolipoproteins A-1 and B were measured immunoturbidimetrically (Orion Diagnostica, Espoo, Finland) and c-reactive protein by latex turbidimetric immunoassay (Wako Chemicals GmbH, Neuss, Germany). In the same blood samples, serum IgA tissue transglutaminase antibodies were measured with an ELISA method [35]. In samples with a level above the suggested cut-off level of 8 AU/mL, IgA anti-endomysium antibodies were determined.

Table I. Health characteristics of subjects with silent coeliac disease and controls.

	Silent coeliac disease		Controls		
	n (21)	%	*n* (2219)	%	Significance
Height cm (±SD)	171.6±8.7		172.1±9.1		$p=0.792$
Weight kg (±SD)	73.1±14.3		74.6±16.0		$p=0.670$
Daily prescription medications	1	4.8	621	28.0	$p=0.014$
Daily vitamins or alternative medications	7	33.3	668	29.8	$p=0.442$
Low back pain in past 12 months	17	81.0	1490	66.3	$p=0.116$
Afternoon tiredness	16/20	80.0	1606	71.8	$p=0.720$
Subjects with children	8	38.1	1221	54.4	$p=0.204$

Table II. Distribution of diagnostic groups in the 660 subjects reporting a medical diagnosis.

Diagnostic group	Silent coeliac disease		Controls		Significance
	n (6)	%	*n* (654)	%	$p = 0.552$
Malignant	0	0	0	0	
Endocrine	0	0	38	5.8	
Deficiency states	1	16.7	20	3.1	
Psychiatric	1	16.7	65	9.9	
Cardiovascular	0	0	36	5.5	
Connective tissue	0	0	30	4.6	
Allergic	2	33.3	289	44.2	
Other	2	33.3	176	26.9	

Subjects with transglutaminase antibodies >10 AU/mL and endomysium antibody titre >50 were considered to have silent or untreated CD. To identify medical or other risks associated with sCD, all the other data collected from these subjects were compared with data for the rest of the study cohort, which served as controls. The significance of the observed differences between the groups was calculated using analysis of variance or chi-square test, with Pearson's continuity correction of the chi-square test where applicable. Logistic regression analysis was used to study the interdependence of the observed differences.

Results

Twenty-one subjects (11 women) with elevated transglutaminase and endomysium antibodies were identified and placed in the untreated sCD group. One of these reported in the questionnaire having CD, but obviously did not adhere to the gluten-free diet and was thus included in the untreated sCD group in the risk analysis. Of the rest of the study population, eight reported having CD and following gluten-free diet. Thus the prevalence of undiagnosed sCD in this cohort was 9.3/1000 (20/2142) and the prevalence of diagnosed CD 3.7/1000 (9/2142).

The subjects with sCD did not differ from the controls in age or sex distribution. Table I describes the main differences in subjective health issues between the sCD subjects and controls. Physical activity and participation in sports was evaluated by 5, dietary habits by 20, alcohol consumption by 13 and tobacco use by 16 questionnaire items, with no differences found between the groups. Altogether 660 subjects reported having a disease diagnosed by a doctor (Table II). No excess of autoimmune, malignant, or allergic diseases was observed in the subjects with sCD. Blood pressure measurements were not different for the two groups. Likewise, blood glucose and C-reactive protein levels did not differ between the groups. Notable laboratory findings are listed in Table III.

Early school performance of sCD subjects did not differ from that of the control group, with similar percentages graduating from primary and secondary school. In further studies, however, the academic performance of sCD subjects was inferior to that of the controls, the difference reaching statistical significance (Table IV). Employment rate as well as occupational classification and socio-economic status (Table V) suggested a uniform tendency to underachievement by the sCD subjects.

Discussion

We report a novel finding in untreated sCD: underachievement in education, probably associated with lower occupational and socio-economic status. Because of certain restrictions on our study, we were unable to confirm the presence of CD in the sCD subjects by intestinal biopsy. The extreme sensitivity of the serological methods, as has been demonstrated in previous studies [36], allows us to be confident, however, that the screening identified nearly all subjects with sCD. In an earlier study using the same methodology, 11 of 12 subjects with similarly positive coeliac antibodies were demonstrated to have duodenojejunal lesions compatible with CD [14]. In the study by Mäki [16], 25 of 27 (93%) transglutaminase and endomysium antibody-positive subjects also had CD confirmed by intestinal biopsy. The prevalence of probable coeliac patients in our cohort, either diagnosed earlier or in the present screening (1 in 74), is close to that for

Table III. Laboratory investigations in silent coeliac disease subjects and controls (mean ± standard deviation).

	Silent coeliac disease ($n = 21$)	Controls ($n = 2262$)	Significance
Serum cholesterol mmol/L	5.06 ± 1.03	5.16 ± 0.98	$p = 0.663$
HDL cholesterol mmol/L	1.12 ± 0.25	1.29 ± 0.32	$p = 0.150$
LDL cholesterol mmol/L	3.18 ± 0.97	2.80 ± 0.81	$p = 0.080$
Triglycerides mmol/L	1.21 ± 0.24	1.34 ± 0.86	$p = 0.483$
Apolipoprotein A-I g/L	1.35 ± 0.24	1.50 ± 0.26	$p = 0.008$
Apolipoprotein B g/L	1.08 ± 0.26	1.06 ± 0.27	$p = 0.758$

Table IV. Highest level of education obtained by subjects with silent coeliac disease.

	Silent coeliac disease		Controls		
Highest level of education	($n=19$)	%	($n=1883$)	%	Significance $p=0.047$
Vocational school	14	73.7	742	39.4	
Junior college	3	15.8	551	29.2	
Vocational college	1	5.3	162	8.6	
University studies	0	0	135	7.2	
University degree	1	5.3	293	15.6	
Years of education		13.52 ± 2.28		14.58 ± 3.09	$p=0.119$

Table V. Employment status, occupation and socio-economic status of subjects with silent coeliac disease.

	Silent coeliac disease		Controls		
Employment status	*n* (21)	%	*n* (2230)	%	Significance $p=0.240$
Full time work or study	16	76.2	1818	81.5	
Unemployed or disabled	3	14.3	128	5.7	
Other (e.g. housewife, military service)	2	9.5	284	12.7	
Occupational classification	*n* (18)	%	*n* (2016)	%	$p=0.112$
Groups 1–3 (e.g. senior official, manager, professional, technician)	5	27.8	904	44.8	
Groups 4–9 (e.g. clerk, care, service and farm workers, plant and machine operators)	13	72.2	1112	55.2	
Socio-economic status	*n* (17)	%	*n* (1902)	%	$p=0.164$
Classes 1–3 (e.g. self-employed, upper level employee, administrative and professional)	3	17.6	603	31.7	
Classes 4–5 (e.g. lower level employees, manual workers)	14	82.4	1299	68.3	

antibody positivity and having the HLA haplotype associated with coeliac disease (1 in 67) [16]. It is therefore likely that our sCD group truly reflects the natural course of asymptomatic CD. The observed lipid profile of sCD subjects resembles that described for active CD [37,38], further suggesting that the subjects do have ongoing intestinal disease.

The subjects with sCD apparently experience no subjective disease symptoms, as their medical concerns, use of prescription medicines or use of alternative medications, were not more prevalent than in the control population, a finding in accordance with earlier observations [17]. We did not identify classical medical complications such as autoimmune or malignant disorders in the subjects with sCD. They did not differ in stature or weight from the control population, a finding in keeping with an earlier study on diabetic children with CD diagnosed through screening [39]. The growth delay of 7-year-old sCD subjects described by Bingley et al. [21] may perhaps be explained by the different proportions of diagnosed and treated CD in the study cohorts: 3.7/1000 in the present study compared with just 0.9/1000 in the study by Bingley et al.

Underachievement in education has not been described in CD. The disruptive behavioural and depressive disorders described in children and adolescents with untreated CD could affect school performance in teenage years. In fact, many of the patients in our previous studies [7,8] reported poor school marks before CD diagnosis and treatment (P. Pynnönen, pers. comm.). The psychiatric or cognitive problems of untreated CD could conceivably lead to poorer secondary school performance, thus precluding college or university entry.

Our findings suggest that the socio-economic status of sCD subjects is affected, a finding not observed in a considerably larger study by West et al. [17]. However, for socio-economic characterization we used only the personal data of the subjects, and not the achievements of their spouses, which we feel are irrelevant in determining the subjects' capabilities. Although none of our findings in regard to employment, occupation and socio-economic status of the subjects (Table V) were of statistical signifi-

cance, the similar trend in results of the three different evaluations supports the suggestion of underachievement of sCD subjects in working life as well.

We infer that underachievement in the group with positive coeliac serology is caused by CD. Whether this is a serious enough problem to warrant population screening programmes is a question for the future, after long-term follow-up of larger numbers of sCD subjects.

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