Peer reviewed article

Prevalence of asymptomatic celiac disease in adolescents of eastern Switzerland

Regula Rutz[a], *Eva Ritzler*[b], *Walter Fierz*[b], *Denise Herzog*[a]

[a] Ostschweizer Kinderspital, St. Gallen, Switzerland
[b] Institute for Clinical Microbiology and Immunology, St. Gallen, Switzerland

Summary

Background: The prevalence of symptomatic CD in Switzerland is thought to be 1 in 1,000 inhabitants. As in other countries, oligo- and asymptomatic CD is being diagnosed with increasing frequency in all age groups. *Aim*: To assess the prevalence of asymptomatic CD in adolescents in eastern Switzerland.

Method: Between September 1999 and July 2000 total serum IgA titres, anti-endomysium IgA (EMA) titres and anti-human tissue transglutaminase IgA (hTTG) titres were measured in the serum of healthy 11- to 18-year-old Swiss lower and upper secondary school students.

Results: Of the 1,450 students (871 f = 60.1%, CI 95%) tested, 11 (10 f) had elevated levels of both EMA and TTG. The diagnosis of CD was confirmed in eight of these students by mucosal jejunal morphology (Marsh III); one exhibited normal histology. Two of the 11 students refused to undergo mucosal biopsy. None of the students, however, had symptoms suggestive of CD, nor were they stunted or underweight, and none of them had family members with known CD. All of the eight students with enteropathy went on a gluten-free diet and felt subjectively better than on a normal diet. Of the remaining students, 38 (2.6%) had family members with known CD. None of those with the relevant family history had elevated EMA or TTG levels.

Conclusion: Asymptomatic CD is common. It occurs in 1 in 132 (0.75%) Swiss adolescents. The absence of subjectively recognisable symptoms suggestive of family history or other risk factors makes it difficult to diagnose this type of CD.

Key words: coeliac disease; asymptomatic; prevalence; Switzerland; adolescents

Introduction

Coeliac disease (CD) is an autoimmune enteropathy characterised by chronic inflammation of the small intestinal mucosa and by the presence of typical autoantibodies. CD develops in genetically predisposed individuals after mucosal contact with gluten and secondarily to hitherto unknown triggering factors [1, 2]. Infants with CD exhibit symptoms of malnutrition, whereas only 30–40% of adults with the disease have such symptoms [2]. Adult coeliac patients tend to remain asymptomatic or oligosymptomatic. However, the increased risk of autoimmune diseases and intestinal lymphoma or carcinoma in individuals with CD calls for screening on the slightest suspicion and for the disease to be treated even when there are no symptoms [3, 4]. Screening studies have therefore been performed in several countries which show that 0.03–0.046% of Italian adolescents [5, 6], 1.06% of Sardinian schoolchildren [7], 0.05% of Dutch [8] and 2% of Swedish infants [9] have asymptomatic CD. To make these screening studies as sensitive as possible they were carried out using anti-endomysium IgA combined with either anti-gliadin IgA or anti-tissue transglutaminase IgA [10, 11]. The aim of the present study is to assess the prevalence of asymptomatic CD in Swiss adolescents in a rural area with a low migration rate. The incidence of symptomatic CD in this region was estimated to be 1 in 1,165 live-born children between 1966 and 1975 [12].

Financial support: The study was supported by awards from the pharmaceutical companies Milupa, Nestlé, Novartis and Solvay.

Methods

With an estimated CD prevalence of 1–5‰ in adolescents, students aged between 12 and 18 appeared to be both a highly suitable and homogeneous test population. A total of 120,000 people aged 0–19 live in the Canton of St. Gallen, 22,000 of whom attend either one of the canton's 108 lower secondary schools or one of its 8 upper secondary schools [13]. Thus, 1,400 samples (CI 95%) were needed to calculate the prevalence of asymptomatic CD. After the aims and procedure of the study had been approved by the ethics committee, the schools' head teachers and the public health authority, students from randomly selected schools were informed of the study by post and sent a questionnaire and a consent form. The questionnaire asked for names, birth date and present height and weight, and sought information on intermittent abdominal pain, constipation, diarrhoea, known chronic diseases and family history of coeliac disease. Capillary blood samples were taken during the school day from consenting volunteer students aged 12–18. Known coeliac disease was an exclusion criterion. First, anti-endomysium IgA (EMA) titres were assessed using indirect immunofluorescence on monkey oesophagus tissue (Nova Lite, Inova Diagnostics, Zurich), anti-tissue transglutaminase IgA (TTG) was measured by an ELISA test using guinea pig antigen (Quanta Lite tTG ELISA Kit, Inova Diagnostics), and total serum IgA titres were measured using turbidimetry (Unimod 3, Roche Diagnostics, lower threshold value 0.2 g/l). The same blood samples were later retested using recombinant human antigen (Celikey® human recombinant anti-tissue transglutaminase IgA Antibody Assay [hTTG], Pharmacia Diagnostics, Dübendorf). Second, venous blood samples were taken from those who tested positive for EMA and hTTG to measure anti-gliadin IgG (AGG) and IgA (AGA) (Quanta Lite, Inova Diagnostics) and to confirm the EMA and hTTG-IgA titres. As a third step, individuals in whom the disease was suspected after the first tests and confirmed by the later test were advised to undergo a small intestinal mucosa biopsy under general anaesthesia (fig. 1). Patients with asymptomatic CD were recommended to adopt a gluten-free diet. Three months after the beginning of dietary treatment the subjective evaluation of dietary effects and dietary compliance were assessed by telephone interview.

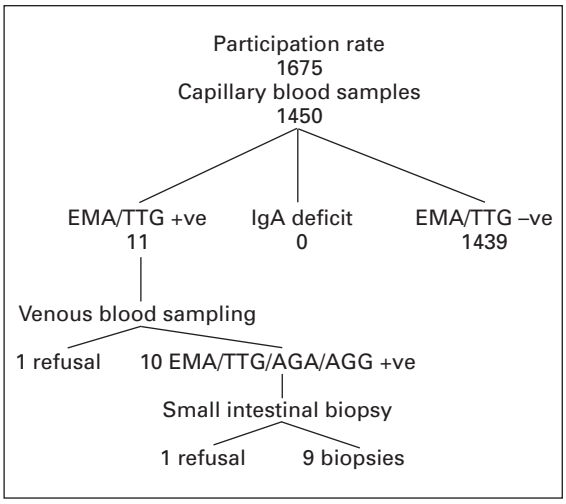


Figure 1

Flow chart of the different steps in the investigation. EMA: anti-endomysium antibody; TTG: anti-tissue transglutaminase antibody; AGG: anti-gliadin IgG antibody; AGA: anti-gliadin IgA antibody.

Statistics

The SPSS program was used to calculate sample size. Taking into account a 5‰ estimated prevalence of asymptomatic CD, a 1‰ known prevalence of symptomatic CD, an expected power of 80% and a confidence interval of 95%, the required sample size was 1,400 volunteers. Mann-Whitney U test was used to compare groups with ordinal and Fisher's exact test to compare groups with categoric data (Statview program). All results are given with a 95% confidence interval.

Results

Screening was carried out in 17 participating schools (19 invited), attended by 6,073 students aged 12–18, between September 1999 and June 2000. The participation rate was 27.5%, with 1,675 volunteers (235 = 14% of non-Swiss nationality). Finally, 1,450 students (23.8%; 579 [39.9%] male, 871 [60.1%] female) were available for blood tests on the prearranged day. A total of 253 (14%) of the participating volunteers (present for blood tests 214 = 14.7%) were citizens of countries other than Switzerland, chiefly Eastern Europe (55.3%), Southern Europe (20%), Near East countries (11.9%), Asia (3.7%), as well as two black and 3 Singalese adolescents. Students of school years higher than the tenth were mainly of Swiss origin.

Eleven students (two of Yugoslav origin), one male and ten females, had positive EMA and/or TTG. In ten of the 11 individuals with elevated autoantibody titres for EMA, we also measured hTTG, AGG and AGA in venous blood, confirming the results of the first test in each case (fig. 1). One female student refused any further tests. Nine of the ten students with positive autoantibodies subsequently underwent biopsy of the small intestinal mucosa. Eight of the nine had enteropathy of type III according to Marsh's criteria, the other exhibiting normal mucosal histology (table 1). Given the heightened specificity and sensitivity of combined testing for coeliac disease using EMA and TTG [10, 11], we included the two positive individuals who did not undergo biopsy in our prevalence calculation as well as the student with normal mucosal histology, calling it latent coeliac disease [14, 15]. Calculated prevalence was 0.75% or 1 in 132 adolescents.

All capillary blood samples were first tested for TTG using guinea pig antigen, but as there were a number of low positive results all the samples were retested for TTG using human recombinant antigen. This was carried out to establish the final results. Ten students with asymptomatic CD were recommended to go on a gluten-free diet. Three months after beginning they were interviewed by telephone about how they felt on a gluten-free diet and about their compliance. All of them reported non-specific improvement of physical condition

but were not willing to continue on a gluten-free diet.

We found no difference in height or weight between students with or without asymptomatic coeliac disease (table 2). No abdominal pain (other than during menstruation) and no stool irregularities (constipation, diarrhoea) were mentioned in either group.

In 49 students (3.4%) anti-TTG autoantibody levels within the same serum sample were found to be elevated when using guinea pig antigen but normal when using recombinant human antigen. None of these students had an elevated EMA level. Venous blood samples from six of the 11 students with moderately elevated levels of TTG were retested for AGA, AGG, EMA and hTTG, and none of these had elevated autoantibody titres. The other five refused to take any further tests, and, along with the remaining 38 students, were considered CD negative.

Total IgA was <0.2 g/l in nine students, and four of these students consented to AGG testing. None of them had elevated AGG levels.

53 students (3.1%) of the 1,675 who volunteered had family members with known coeliac disease. Of these 53 students, 38 (2.6%) had given blood samples and all of them had normal EMA/TTG and total IgA. None of the 11 students with asymptomatic CD was aware of a family member with CD.

Discussion

The primary aim of this study was to assess the prevalence of oligo- and/or asymptomatic CD among adolescents in a rural region with a low migration rate. Tests for EMA, hTTG and total serum-IgA [16, 17] indicated a prevalence of 0.75% or 1 in 132 adolescents. This type of antibody-testing was chosen because of the additive high sensitivity and specifity of EMA and TTG, thereby avoiding many false positive results. The prevalence found in this study is similar to that

Table 1
Individuals with asymptomatic coeliac disease.

Sex	age (yr)	height (cm)/weight (kg) z-score	EMA 1/2	TTG 1/2	IGAg/l	AGA	AGG	histology jejunal
F	14.5	157/65 z = –1/2	>20/>20	44/32	2.37	38	24	Marsh III
F	14.3	155/44 z = –1.7/–1	>80/>5	26/59	1.73	<20	<20	normal histology
F	16.7	166/67 z = 2/1	>20	>100	1.2	nd	nd	no biopsy
F	14.5	180/63 z = 2/3	>5/>20	6	2.3	<20	<20	Marsh III
F	13.6	155/38 z = –1.7/–1	>5/10	9	1.26	<20	<20	Marsh III
F	17.0	167/59 z = 1/1	>5/<5	12/92	1.4	46	158	Marsh III
F	14.6	168/52 z = 1/2	>20/>20	>244/>131	1.61	>161	55	Marsh III
F	14.5	150/38 z = –2/–2	<5/>5	>195/>131	0.95	<20	20	Marsh III
F	16.8	164/45 z = 1/–2	160/160	>217	2.2	36	140	Marsh III
F	17.3	164/64 z = 1.7/1	80/>20	185	2.26	62	26	Marsh III
M	17.4	176/64 z = 1/1	7/<5	23/11	2.85	<20	<20	no biopsy

Normal values: EMA <5, AGG + AGA <20, TTG <5

Table 2
Height and weight z-scores and gender of students with and without CD.

	students with CD (n = 11)	students without CD (n = 1439)	p
Weight: z-score (median + range)	+ 1.7 (–2 – +3)	+ 1 (–2.6 – + 4.4)	ns*
Height: z-score (median + range)	+ 1.35 (–2 – +2)	– 1 (–2.65 – + 3.06)	ns*
Gender	10 female, 1 male	861 female, 578 male	0.059**

* Mann Whitney U test; ** Fishers exact test

found in Scandinavian countries (up to 2%) [11, 18, 19], Ireland (0.8%) [20], Italy (0.03–1.06%) [7, 21] and North America (0.4%) [22]. Thus, about 1% of the adolescent population of those countries has CD. The reasons for this alarmingly high prevalence are not known, nor do we know whether this is an old problem that has only now come to light or indeed an entirely new phenomenon.

The relatively low participation rate of 24% was mainly due to the blood test, which many students were afraid of. Additionally, the participation rate was strongly influenced by classroom peer pressure and the motivation provided or authority wielded by individual teachers.

We included all the students with both elevated TTG and EMA in the CD group, even though two of them refused small intestinal biopsy and one student had normal histology. The two without small intestinal histology should be considered to have at least latent (elevated autoantibody titres without histological abnormalities) or silent (no symptoms, but histological abnormalities) coeliac disease [14, 15], as should the student with normal histology. It is widely acknowledged that a patient can be autoantibody-positive for months before enteropathy is histologically visible [23, 24].

Individuals with newly diagnosed CD went on a gluten-free diet for a three-month trial period and felt subjectively better during that time. However, this improvement was not felt to be great enough to motivate them to continue the diet, even though the importance of a lifelong gluten-free diet was explained to them. The most significant reason for giving up the diet was the fact that gluten-free products are both expensive and difficult to obtain. They were therefore informed of the risks inherent in untreated CD and advised to consult their family doctor whenever symptoms appeared.

There was no difference in height, weight, stool habits or abdominal pain episodes between students with elevated and those with normal autoantibody titres, but in students with asymptomatic CD there was a female predominance which approached statistical significance (table 2). However, larger studies are necessary to determine whether female gender is a more important risk factor for asymptomatic CD than for autoimmune disease in general [25].

None of the students with asymptomatic CD had family members with known CD, whereas 2.6% of participants with normal autoantibodies had. Given that Auricchio found that 10% of first-year schoolchildren related to CD patients have coeliac disease [26], that Catassi [21] established a ratio of one known case to every seven undiagnosed cases of CD in Italy, and that the mean family size in the Canton of St. Gallen is between four and five persons, we did not expect to find that the only students who had known family members with CD did not themselves have asymptomatic CD, and that those 11 students who had asymptomatic CD diagnosed for the first time by the study did not have any known family members with the disease. Wider screening studies will be necessary to ascertain whether CD occurring in families and asymptomatic CD are different manifestations of the same disease, possibly dependent on genetic factors other than HLA class II haplotypes, as was found to be the case for dermatitis herpetiformis [27].

We found a number of falsely elevated anti-TTG-IgA titres when using guinea pig antigen, whereas anti-hTTG-IgA positivity correlated well with anti-EMA-IgA positivity. This good correlation using hTTG has also been established by other groups [28–30] and has been attributed to the purity of the antigen used both in screening studies and in groups with known coeliac disease.

In conclusion, we found a high prevalence of asymptomatic CD in adolescents of Canton St. Gallen. This unexpectedly high prevalence raises the question of population screening. However, CD can appear at any age and thus there is no time-point for autoantibody screening. Inclusion of HLA-DQ2 [31] in newborn screening is controverted, since only positive individuals develop CD. However, ethical and economic considerations argue against this type of screening. Further research for risk factors is therefore necessary.

Acknowledgement: The participating schools played a major organising role and made rooms available for blood sampling.

Correspondence:
D. Herzog, M.D.
Ostschweizer Kinderspital
Claudiusstrasse 6
CH-9006 St. Gallen
E-Mail: deniseherzog@hotmail.com

References

1 Trier JS. Celiac sprue. N Engl J Med 1991;325:170–19.
2 Marsh NW. Gluten, major histocompatibility complex, and the small intestine: a molecular and immunobiological approach to the spectrum of gluten sensitivity. Gastroenterology 1992; 102:330–54.
3 Corrao G, Corazza GR, Bagnardi V, Brusco G, Ciacci C, Cottone M, Guidetti CS, Usai P, Cesari P, Pelli MA, Loperfide S, Volta U, Calsabro A, Certo M. Club del Tenue Study Group. Mortality in patients with coeliac disease and their relatives: a cohort study. Lancet 2001;358:356–61.
4 Schweizer JJ, Oren A, Mearin MC. Working group for celiac disease and malignancy of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Cancer in children with celiac disease. A survey of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2001;33:97–100.
5 Catassi C, Fabiani E, Rätsch IM, Coppa GV, Giorgi PL. Celiac disease in the general population: should we treat asymptomatic cases. J Ped Gastroenterol Nutr 1997;24:S10–3.
6 Catassi C, Ratsch IM, Fabiani E, Rossini M, Bordicchia F, Candela F, et al. Coeliac disease in the year 2000: exploring the iceberg. Lancet 1994;343:200–3.
7 Meloni G, Dore A, Fanciulli G, Tanda F, Bottazzo GF. Subclinical coeliac disease in schoolchildren from northern Sardinia. Lancet 1999;353:37.
8 Csizmadia CGDS, Mearin ML, Mary B, vBlomberg E, Brand R, Verlove-Vanhorick SP. An iceberg of childhood celiac disease in the Netherlands, Lancet 1999;353:813–4.
9 Carlsson AK, Axelsson IE, Borulf SK, Bredberg AC, Ivarsson SA. Serological screening for celiac disease in healthy 2.5-year-old children in Sweden. Pediatrics 2001;107:42–5.
10 Scott H, Brandtzaeg P. Endomysial autoantibodies. In: Peter JB, Shoenfeld Y, eds. Autoantibodies. Amsterdam: Elsevier Science, 1996:237–44.
11 Chan AW, Butzner JD, McKenna R, Fritzler MJ. Tissue transglutaminase enzyme-linked immunosorbent assay as a screening test for celiac disease in pediatric patients. Pediatrics 2001; 107:E8.
12 van Stirum J, Baerlocher K, Fanconi A, Gugler E, Tonz O, Shmerling DH. The incidence of coeliac disease in children in Switzerland. Helv Paediatr Acta 1982;37:421–30.
13 Office for statistics of the canton St. Gallen, census 1990.
14 Troncone R., Greco L, Mayer M, Papro F, Caputo N, Micillo M, et al. Latent and potential coeliac diseases. Acta Paediatr Suppl 1996;412:10–4.
15 Troncone R. Latent coeliac disease in Italy. The SIGEP Working group on latent coeliac disease. Acta paediatr 1995;84: 1252–7.
16 vBlomberg BME, Csizmadia GDS, Kromhout A, Holterhues T, Verkerk PH, Pena AS, et al. Screening tests for celiac disease in the general population: EMA or tTG? J Ped Gastroenterol Nutr 2001;32:362.
17 Grodzinsky E, Hed J, Skogh T. IgA antiendomysium antibodies have a high positive predictive value for celiac disease in asymptomatic patients. Allergy 1994;49:593–7.
18 Ascher H, Krantz I, Kristiansson B. Increasing incidence in coeliac disease in Sweden. Arch Dis Child 1991;66:608–11.
19 Kolho KL, Farkkila MA, Savilahti E. Undiagnosed celiac disease is common in Finish adults. Scand J Gastroenterol 1998; 33:1280–3.
20 Johnston SD, Watson RG, McMillan SA, Sloan J, Love AH. Prevalence of celiac disease in Northern Ireland. Lancet 1997; 350:1370.
21 Catassi C, Fabiani E, Ratsch IM, Coppa GV, Giorgi PL, Pierdomenico R, et al. The coeliac iceberg in Italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. Acta Paediatr Suppl 1996;412:29–35.
22 Not T, Horvath K, Hill ID, Partanen J, Hammed A, Magazzu G, et al. Celiac disease risk in USA: high prevalence of antiendomysium antibodies in healthy blood donors. Scand J Gastroenterol 1998;33:494–8.
23 Maki M, Holm K, Koskimies S, Hallstrom O, Visakorpi JK. Normal small bowel biopsy followed by celiac disease. Arch Dis Child 1990;65:1137–41.
24 Corazza GR, Andreani ML, Biagi F, Bonvicini F, Bernardi M, Gasbarrini G. Clinical, pathological, and antibody pattern of latent celiac disease: report of three adult cases. Am J Gastroenterol 1996;91:2203–7.
25 Bode S, Gudmand-Hoyer E. Symptoms and haematologic features in consecutive adult coeliac patients. Scand J Gastroenterol 1996 Jan;31:54–60.
26 Auricchio S, Mazzacca G, Tosi R, Visakorpi M, Maki M, Polanco I. Coeliac disease as a familial condition: identification of asymptomatic coeliac patients within family groups. Gastroenterol Int 1988;25–31.
27 Holopainen P, Mustalahti K, Uimari P, Collin P, Mäki M, Partanen J. Candidate gene regions and genetic heterogeneity in gluten sensitivity. Gut;2001;48:696–701.
28 Bürgin-Wolff A, Peterson CJ, Hadziselimovic F, Dahlbom I. Antihuman tissue transglutaminase IgA antibodies versus endomysium antibodies for monitoring and diagnosis of celiac disease. J Ped Gastroenterol Nutr 2001;32:376.
29 Fabiani E, Rondina C, Peruzzi E, Galeazzi R, Catassi C. IgA anti-guinea pig versus anti-human tissue transglutaminase for coeliac disease screening. J Ped Gastroenterol Nutr 2001;32: 355.
30 Wolters VM, Moulaert AF, Brooimans RA, DeSchryver JEAR, Rijkers GT, Houwen RHJ. Human tTG ELISA outperforms guinea pig based tTG and EMA when screening for celiac disease in patients with GI complaints. J Ped Gastroenterol Nutr 2001;32:379.
31 Sollid L, Thorsby E. HLA susceptibility genes in celiac disease: genetic mapping and role in pathogenesis. Gastroenterology 1993;105:910–22.

Swiss
Medical Weekly

Official journal of
the Swiss Society of Infectious disease
the Swiss Society of Internal Medicine
the Swiss Respiratory Society

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

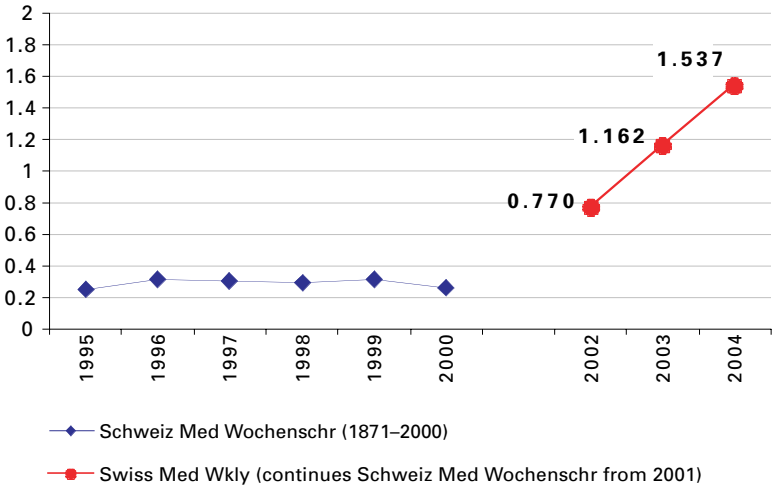
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch