Population-Based Screening for Selective Immunoglobulin A (IgA) Deficiency in Lithuanian Children Using a Rapid Antibody-Based Fingertip Test

Vaidotas Urbonas, Jolita Sadauskaite, Rimante Cerkauskiene, Arvydas Kaminskas, Markku Mäki, Kalle Kurppa

Background: Selective immunoglobulin A (IgA) deficiency is the most common inherited immunodeficiency disorder worldwide. An early diagnosis is advocated because of the increased risk of infections, autoimmune diseases, and allergic reactions. We investigated the usefulness of a rapid point-of-care test in detecting for IgA deficiency in a population with a previously unknown prevalence.

Material/Methods: Altogether, 1000 children aged 11–13 years from randomly selected Lithuanian schools were enrolled. A point-of-care test with a fingertip sample was used to screen for the presence of IgA deficiency in children whose parents gave consent. Those with suspected IgA deficiency were referred to hospital for further clinical examination and confirmation of the diagnosis. In addition, their medical histories were compared with those of 30 age- and sex-matched healthy controls.

Results: IgA deficiency was suspected in one girl and in three boys on the basis of the rapid test, and the diagnosis was confirmed for all four cases (prevalence 0.4%, 95% confidence interval 0.16–1.02%). There was no difference in disease history or complications between IgA-deficient children and healthy controls.

Conclusions: The rapid antibody test is a practical and accurate method to diagnose selective IgA deficiency in children. The prevalence of IgA deficiency among Lithuanian schoolchildren is 1:250.

MeSH Keywords: Child • IgA Deficiency • Mass Screening • Prevalence

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/898269
Background

Selective immunoglobulin A (IgA) deficiency is the most common inherited immunodeficiency disorder worldwide. It is diagnosed when the total IgA concentration is below 0.05–0.07 g/L in children over four years of age and when IgG and IgM are normal [1–3]. The global prevalence of IgA deficiency varies from 1:134 to 1:18,500 depending on the population in question [4,5]; however, in many countries, as in Lithuania, the prevalence is still unknown. Approximately 90% of individuals with IgA deficiency have no specific symptoms or signs [6]. Notwithstanding this often subclinical presentation, they carry a markedly increased risk of infections and long-term complications [7–9]. The risk of autoimmune diseases is also increased, in particular celiac disease, which is ten times more common in individuals with IgA deficiency than in the general population [10,11]. Celiac disease often goes unrecognized in these patients because they do not express IgA class transglutaminase 2 antibodies (TG2-ab) and are thus missed in routine screening [11]. In fact, approximately 10% of IgA-deficient blood donors may have unrecognized celiac disease. IgA-deficient individuals may also develop anti-IgA antibodies, which cause anaphylactic reactions upon transfusion of IgA-containing blood products [12]. The aforesaid aspects emphasize the importance of finding these subjects as early as possible. Large-scale laboratory-based testing is, however, impractical for this purpose. Interestingly, a rapid point-of-care test for celiac disease requiring only a fingertip sample has recently been developed [13]. This sensitive test simultaneously measures the presence of blood IgA and could thus be used for the screening of IgA deficiency in outpatient settings.

We sought to establish the utility of the rapid fingertip test in population-based screening for selective IgA deficiency among Lithuanian schoolchildren. At the same time we were able to assess the previously unknown prevalence and clinical presentation of the condition in this population.

Material and Methods

Participants and study design

The study was carried out in Vilnius University Children’s Hospital and the Vilnius University Faculty of Medicine, Lithuania, from January 2009 to March 2010. Six separate secondary schools in the hospital catchment area were randomly selected for study enrolment. Altogether, 1583 fifth- to seventh-grade students (746 girls and 837 boys) aged 11–13 years were asked to participate in voluntary testing for IgA deficiency and celiac disease by a well-instructed fifth-course medical student from the Vilnius University Medical Faculty. Of these subjects, a total of 1038 (65.5%) parents and 1026 (64.8%) children gave written informed consent to participate. Only children with both personal and parents’ agreement were included. Twenty-six of the consenting pupils were absent from school at the time of the investigation. Thus, exactly 1000 children (496 girls and 504 boys) comprised the final cohort.

The study protocol and recruitment were approved by the Lithuanian Bioethics Committee. All procedures involving human participants were in accordance with the ethical standards of the committee and with the 1964 Helsinki declaration and its later amendments. All study children and their parents gave written informed consent to participate.

IgA deficiency and celiac disease testing

The presence of IgA deficiency was investigated by a commercial point-of-care test (Biocard™ Celiac Test, Ani Biotech, Vantaa, Finland) according to the manufacturer’s instructions. The Biocard test is a combined qualitative immunochromatographic assay measuring simultaneously the presence of blood IgA and celiac disease-specific IgA class TG2-ab. Cutoff for negative IgA is set at a blood value below 0.2 g/L. During the investigation, 10 microliters of blood were taken from the child’s finger with a capillary tube, placed in a test tube with buffer solution, and shaken in order to mix the capillary blood with the buffer. Next, three drops of the mixture were taken from the test tube and dropped into the pit of a disposable chromatographic plate, and results were assessed after 2–5 minutes. If a child was IgA sufficient, one control strip appeared in the chromatographic field; if the test field remained clear, the child was suspected of IgA deficiency. The Biocard point-of-care test has previously been shown to have 78.1% sensitivity and 100% specificity for biopsy-proven celiac disease [14] and 96.7% sensitivity and 93.5% specificity compared with the serum TG2-ab and endomysial antibody tests from stored patient samples [13]. There are no previous studies investigating its use in IgA-deficiency screening.

Clinical investigations

If the presence of IgA deficiency was suspected, the parents were informed and the child was referred to Vilnius University Children’s Hospital for thorough clinical investigation and further laboratory sampling. All clinical investigations were performed by the same experienced pediatrician (VU). The serum IgA, IgM, IgG, and IgE concentrations were measured in the hospital laboratory using an immunoturbidimetric assay with routine methodology (analyzer: Cobas Integra 400 Plus, Roche, Switzerland; reagents: Roche Diagnostics GmbH, Germany). In addition, the total B and T cell counts were examined as part of hospital routine to exclude other immune deficiencies. According to the recommendations of North American and European guidelines, selective IgA deficiency was diagnosed.
if the IgA concentration was less than 0.07 g/L and other immunoglobulins and B/T cell counts were normal [1,15].

Possible previous hospital records of the children with IgA deficiency were carefully checked. In addition, their health records were acquired from primary health care with permission, and the case histories were further compared with 30 age- and sex-matched IgA-competent controls randomly selected from the original study cohort. Besides routine clinical data, the frequency and presence of complicated disease courses (in particular, gastrointestinal tract infections, upper and lower respiratory tract infections, diseases, allergic reactions, and autoimmune diseases) were registered, as well as possible adverse reactions to vaccines and blood products.

Statistics

At time of the study 112,990 children aged 11–13 years lived in Lithuania; of these, 15,138 lived in Vilnius [16]. Because we aimed to establish the prevalence of IgA deficiency with 90% calculated probability, it was necessary to study 1061 children in the Republic of Lithuania and 1001 in Vilnius. With an estimated participation rate of 60%, six schools with were selected. The study data were analyzed using Epi Info statistics (Centers for Disease Control and Prevention, Atlanta, Georgia, USA) and Statistical Package for the Social Sciences software (SPSS Inc., Chicago, Illinois, USA) programs. The results were given in percentages and absolute numbers. The prevalence rate was calculated by writing the number of cases in the numerator and the figure for the whole population in the denominator. Further, 95% confidence intervals were determined for the calculated prevalence rate.

Results

Altogether, 950 (95%) of the children involved were of Lithuanian ethnicity. The testing procedure was considered easy by both tester and children, and no adverse effects apart from minor fingertip pain were reported. The distribution of the study cohort and the presence of IgA deficiency according to age and sex are shown in Table 1. There were no significant differences between the three age cohorts in the number of children or gender distribution. Based on the Biocard test, IgA deficiency was suspected in one girl and one boy aged 12 years and in two boys aged 13 years. In subsequent laboratory analysis the IgA concentration in all four children was below 0.066 g/L (lowest detectable limit of the assay). Further, serum IgM, IgG, and IgE concentrations as well as B/T cell counts were normal, and the children were not on any medication nor suffered from any other medical condition explaining the finding. Consequently, all four received a diagnosis of selective IgA deficiency (Table 1).

Analysis of the health records of subjects with newly identified IgA deficiency showed that all four had suffered from common infections such as otitis, sinusitis, tonsillitis, nasopharyngitis, laryngitis, or bronchitis from two to four times a year (mean frequency 3.0 per year); the frequency of infections did not differ from that in the IgA-competent controls (mean frequency of corresponding respiratory and ear infections 3.1 per year; data not shown). None of the four IgA-deficient children had suffered from documented gastrointestinal infection, but all had a history of chickenpox and one also of rubella. There were no reported complications after the infections, and antibiotics were used in a single case only for tonsillitis. None of the cases with IgA deficiency had major allergies or adverse reactions to vaccines or blood products. The girl with IgA deficiency had a previous diagnosis of psoriasis (her parents did not suffer from this).

The IgA-deficient children reported no clinical symptoms or signs suggestive of celiac disease or other gastrointestinal disease, but upper gastrointestinal endoscopy with small-bowel mucosal biopsies was offered to all four according to our clinical practice at the time of the study. The endoscopy was performed on two children, which in both cases yielded normal macroscopic and microscopic findings; the other two IgA-deficient children declined the procedure.

Table 1. Distribution of study children according to age and gender and presence of selective IgA deficiency.

| Age (years) | Girls n  | Girls % | Boys n  | Boys % | All n  | All % |
|------------|----------|---------|---------|--------|--------|------|
| 11         | 173      | 17.3    | 166     | 16.6   | 339    | 33.9 |
| 12         | 159      | 15.9    | 175     | 17.5   | 334    | 33.4 |
| 13         | 164      | 16.4    | 163     | 16.3   | 327    | 32.7 |
| 11–13      | 496      | 49.6    | 504     | 50.4   | 1000   | 100.0|
| IgA deficiency* | 1        | 0.2     | 3       | 0.6    | 4      | 0.4  |

* Based on the final diagnosis at the tertiary hospital.

© Med Sci Monit, 2016; 22: 4773-4778

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System]
[ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica]
[Chemical Abstracts/CAS] [Index Copernicus]
Two of the 1000 study children (0.2%) had normal IgA and positive TG2-ab testing results. One (a girl) already had a previous celiac disease diagnosis but was not following a strict gluten-free diet. The other (a boy) was biopsied and found to have celiac disease; he was subsequently placed on a gluten-free diet.

Discussion

The main finding in the present study was that the rapid point-of-care fingertip test is an easy, practical, and accurate method to screen for selective IgA deficiency in an unselected pediatric population. Furthermore, the previously unknown prevalence of IgA deficiency among Lithuanian children was now found to be 1:250.

The main function of IgA is mucosal defense in the airways and intestine, where the body encounters most pathogens and thus needs to mount a fast and effective immunological response. Accordingly, IgA-deficient patients run an increased risk, in particular, of different respiratory and gastrointestinal tract infections [7–10,12,17,18]. Healing of the infections may also be compromised, and complications such as chronic diarrhea and bronchiectasis may follow [7,12,19,20]. Here we found no difference in the frequency or severity of infections between IgA-deficient children and controls. This in itself is no surprise, because these problems usually manifest later in adulthood [9,17,18]. However, there is wide individual variation, and some patients may develop severe infections in infancy. This heterogeneity in clinical presentation might be explained by replacement of IgA functions by other immunoglobulins in some individuals, while in others there might be concomitant deficiencies, for example, in certain IgG subclasses [21,22]. In any case, an early diagnosis of the condition enables prompt recognition of severe infections and hence lowers the risk of long-term complications.

None of the IgA-deficient children in this study was found to have celiac disease, but only two were biopsied and we were not able to measure IgG-class antibodies. The marked overrepresentation of celiac disease in patients with IgA deficiency is clinically important, because recent studies have shown it to be one of the commonest pediatric disorders [23,24]. Because IgA-based tests are used in first-line screening for celiac disease, IgA-deficient subjects are easily missed. These unrecognized cases have, besides the burden of symptoms and unnecessary investigations, an increasing risk of complications such as anemia and poor growth [25]. In these circumstances the rapid test is of great value in allowing simultaneous investigation of the presence of both celiac disease and IgA deficiency. Besides celiac disease, IgA-deficient individuals are also at risk of other autoimmune diseases such as rheumatoid arthritis and myasthenia gravis [1,2]. In the present study the only

| Target population          | Reference |
|----------------------------|-----------|
| Adults, children           | 5         |
| Children 2–16 years        | 32        |
| Children 4 years           | 7         |
| Children                  | 33        |
| Children 2–16 years        | 34        |
| Children                  | 35        |
| Blood donors               | 36        |
| Blood donors               | 37        |
| Blood donors               | 38        |
| Blood donors               | 39        |
| Blood donors               | 40        |
| Blood donors               | 41        |
| Blood donors, pregnant women | 42     |
| Blood donors               | 43        |
| Adults, children           | 44        |
| Blood donors               | 4         |

* Size of the screened population.

Table 2. Prevalence of selective IgA deficiency in different populations from lowest to highest according to previous screening studies.
girl with IgA deficiency had psoriasis. This might be a coincidence, but such a combination has previously been reported, and it is possible that IgA deficiency predisposes to the development of this disorder [26].

Another issue advocating early diagnosis of IgA deficiency is the risk of anaphylactic reactions to transfusion products such as red blood cells and platelets [27]. It has been suggested that such reactions can be prevented by providing blood components lacking IgA collected from IgA-deficient donors [27]. Based on this option, donor registries have been established in the USA and Canada, and also in some countries in Europe and Asia [28–30]. The rapid test could be particularly useful in this setting, on the one hand in excluding IgA deficiency in subjects receiving blood products and on the other hand in screening for possible donors for the registries.

For the first time, we were able to establish the prevalence of IgA deficiency in the Lithuanian population, showing it to be 0.4%. This result is both nationally and ethnically representative, because the country’s population is more than 80% ethnic Lithuanian, and 95% of our cohort were Lithuanians. A comparison with worldwide prevalence figures is presented in Table 2. In general, the Lithuanian prevalence is fairly high, but then again it is close to that in neighboring countries such as Estonia, Sweden, and Finland. The wide global variation very likely reflects differences in genetic predisposition [31]. However, it must be emphasized that in many previous studies only blood donors or hospital-based cohorts were examined, and this may not accurately reflect the true prevalence (Table 2 [32–43]). In contrast, using the rapid test we were able to screen an unbiased sample of the pediatric population.

The major strength of the present study is the well-defined and nationally representative study cohort. An obvious limitation is the small number of IgA-deficient cases, which reduced statistical accuracy and rendered the comparisons of medical histories less useful. In theory it is also possible that we missed some IgA-deficient cases, because not all study children underwent laboratory testing. However, this is unlikely due to the rather high cutoff value of 0.2 g/L in the rapid test. That being said, in this study the tests were read by an experienced reader; the evaluation might be less reliable if undertaken by a layman [44]. Finally, our results should not be generalized to very young children, who may have physiologically low IgA values.

Conclusions

The rapid point-of-care fingertip test significantly reduces the time and costs associated with population screening for IgA deficiency, and is also an accurate and practical means of case finding in outpatient settings. The prevalence of IgA deficiency in the Lithuanian pediatric population is close to that seen in neighboring Baltic and Scandinavian countries.

Conflict of interest

Dr. Markku Mäki is one inventor of the patent, “Methods and Means for Detecting Gluten-Induced Diseases,” USA States Patent Number 7,361,480 – USA, patent granted 22.4.2008; European Patent No. 1390753, European Patent Office 22.10.2008. Finn Medi Oy Ltd, owned by the University of Tampere and Tampere University Hospital, Finland, has commercialized the patent and licensed it to Ani Biotech, which used it to develop the Biocard Celiac Test. Neither Finn Medi Oy nor Ani Biotech was involved in the present study. Drs. Urbonas, Sadauskaite, Cerkaukiene, Kaminskas, and Kurppa declare no conflict of interests.

References:

1. Bonilla FA, Bernstein IL, Khan DA et al: Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol, 2005; 94: 51–63
2. Conley ME, Notarangelo LD, Etzioni A: Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol, 1999; 93: 190–97
3. Geha RS, Notarangelo LD, Casanova JL et al: Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol, 2007; 120: 776–94
4. Kanoh T, Mizumoto T, Yasuda N et al: Selective IgA deficiency in Japanese blood donors: Frequency and statistical analysis. Vox Sang, 1986; 50: 81
5. McGowan KE, Lyon ME, Butzner JD: Celiac disease and IgA deficiency: Complications of serological testing approaches encountered in the clinic. Clin Chem, 2008; 54: 1203–9
6. Yel L: Selective IgA deficiency. J Clin Immunol, 2010; 30: 10–16
7. Cunningham-Rundles C: Physiology of IgA and IgA deficiency. J Clin Immunol, 2001; 21: 303–9
8. Janzi M, Kull I, Sjöberg R et al: Selective IgA deficiency in early life: association to infections and allergic diseases during childhood. Clin Immunol, 2009; 133: 78–85
9. Koskinen S: Long-term follow-up of health in blood donors with primary selective IgA deficiency. J Clin Immunol, 1996; 16: 165–70
10. Cataldo F, Marino V, Ventura A et al: Prevalence and clinical features of selective immunoglobulin A deficiency in coeliac disease: An Italian multicentre study. Gut, 1998; 42: 362–65
11. Collin P, Mäki M, Kyrilikänä O et al: Selective IgA deficiency and coeliac disease. Scand J Gastroenterol, 1992; 27: 367–71
12. Edwards E, Razvi S, Cunningham-Rundles C: IgA deficiency. Clinical correlates and responses to pneumococcal vaccine. Clin Immunol, 2004; 111: 93–97
13. Rahvio T, Kaukinen K, Nemes E et al: Self transglutaminase-based rapid coeliac disease antibody detection by a lateral flow method. Aliment Pharmacol Ther, 2006; 24: 147–54
14. Korponay-Szabó IR, Szabados K, Pusztai I et al: Population screening for coeliac disease in primary care by district nurses using a rapid antibody test: Diagnostic accuracy and feasibility study. BMJ, 2007; 335: 1244–47
15. Notarangelo LD, Fischer A, Geha RS et al: Primary immunodeficiencies: 2009 update. J Allergy Clin Immunol, 2009; 124: 61–78

16. http://db1.stat.gov.lt/statbank/SelectVarVal/Define.asp?Maintable=M30102008&Language= Accessed January 5, 2009

17. Aghamohammadi A, Cheraghi T, Gharagozlou M et al: IgA deficiency: Correlation between clinical and immunological phenotypes. J Clin Immunol, 2009; 29: 130–36

18. Aytekin C, Tuygun N, Gokce S et al: Selective IgA deficiency: Clinical and laboratory features of 118 children in Turkey. J Clin Immunol, 2012; 32: 961–66

19. Chippis BE, Talamo RC, Winkelstein JA: IgA deficiency, recurrent pneumonias, and bronchiectasis. Chest, 1978; 73: 519–26

20. Diez R, Garcia MJ, Vivas S et al: Gastrointestinal manifestations in patients with primary immunodeficiencies causing antibody deficiency. Gastroenterol Hepatol, 2010; 33: 347–51

21. Borst S, Pan-Hammarström Q, Liu C et al: Interleukin-21 restores immunoglobulin production ex vivo in patients with common variable immunodeficiency and selective IgA deficiency. Blood, 2009; 114: 4089–98

22. Plebani A, Carbonara AO, Bottaro A et al: Gene deletion as a cause of associated deficiency of IgA1, IgG2, IgG4 and IgE. Immunodeficiency, 1993; 4: 245–48

23. Myléus A, Ivarsson A, Webb C et al: Celiac disease revealed in 3% of Swedish 12-year-olds born during an epidemic. J Pediatr Gastroenterol Nutr, 2009; 49: 170–76

24. Rezvan H, Ahmadi D, Esmailzadeh S, Dayhimi I: Selective IgA deficiency among healthy voluntary blood donors in Iran. Blood Transfus, 2009; 7: 152–54

25. Feng L: Epidemiological study of selective IgA deficiency among 6 nationalities in China. Zhonghua Yi Xue Za Zhi, 1992; 72: 88–90