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Reliability of varicella history in children and adolescents

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Summary

Question under study: Only limited data are available regarding the reliability of the varicella zoster virus (VZV) history in children and adolescents. Our goal was to determine positive and negative predictive values of varicella history in a prospective cross-sectional study.

Methods: Patients 1–18 years of age who were hospitalised in our institution between 1999 and 2000 were eligible for participation when a blood specimen was taken for any medical reason. Patients with current varicella, immunodeficiency, immunoglobulin treatment in the previous 6 months, or significant language barriers were excluded. After informed consent had been obtained, parents were asked whether their child had a history of varicella (categorized as definite, probable, possible, negative or unknown). Anti-VZV-IgG antibodies were then tested by ELISA (Enzygnost®). If the ELISA result was indeterminate, the specimen was analysed by fluorescent-antibody staining of membrane antigen in VZV-infected cells (FAMA), the serological gold standard.

Results: 449 patients (mean age 6.4 years, median 5.4 years) were enrolled. History of varicella was definite in 234 (52%), probable in 12 (3%), possible in 1, negative in 196 (44%) and unknown in 6 (1%) patients. Overall, 61% (95% CI: 56–65) of patients were positive for VZV antibodies. Seroprevalence was 25%, 68% and 95% in 1–4 year olds (group 1, n = 167), 5–8 year olds (group 2, n = 136) and 9–18 year olds (group 3, n = 146), respectively. The positive predictive value of a definite history of varicella was 98% (95% CI: 96–100) (93%, 100%, and 98% in groups 1, 2 and 3, respectively). The negative predictive value was 85% (95% CI: 80–90), decreasing with age (group 1: 97%; group 2: 77%; group 3: 26%).

Conclusions: The positive predictive value of a history of varicella is high in children and adolescents. In countries where universal immunization against varicella is not recommended, selectively immunizing adolescents with a negative history can reduce the rate of susceptible individuals efficiently.

Key words: varicella; varicella zoster virus; history; immunization; vaccine

Introduction

The reliability of varicella (chickenpox) history is important for designing catch-up immunization strategies for older children and adolescents, where serotesting is the only alternative to presumptive vaccination. While this issue has been extensively studied in adults [1–6], limited data are available in children and adolescents [7–10].

In many European countries, universal childhood immunization against varicella zoster virus (VZV) infections is currently under debate. In Switzerland its implementation is not to be expected in the near future due to lack of acceptance amongst both the general public and physicians [11]. By demonstrating the reliability of a positive history of varicella in older children and adolescents, a selective immunization strategy of those who might still be susceptible could be envisioned as a first step towards decreasing the burden of varicella and its complications. The goal of this study was to evaluate the reliability of a varicella history, compared to the presence of specific anti-VZV IgG serum antibodies in children and adolescents hospitalised in our institution in Basel, Switzerland. Our findings were presented at an international meeting [12] and provided relevant data for the current recommendation in Switzerland to immunize adolescents with an uncertain history for varicella [13].

No financial support declared.

Methods

Study population

This was a cross-sectional study. Patients 1–18 years of age, hospitalised in our institution between 1999 and 2000, were eligible for participation when a blood specimen was taken for any medical reason. Patients with a current VZV infection, immunodeficiency, immunoglobulin treatment in the previous 6 months, or significant language barriers were excluded. According to standard admission procedures in our hospital, parents were asked whether their child had a history of certain childhood infectious diseases including varicella. Furthermore, parents were asked to assess the degree of certainty of the history as definite, probable, possible, negative or unknown. Afterwards, informed consent was obtained from parents and patients (if at least 12 years of age) to determine anti-VZV IgG antibodies in a serum aliquot.

Laboratory assays

IgG serum antibodies against VZV were determined by use of a commercially available ELISA kit (Enzygnost® Anti-VZV/IgG, Dade Behring AG, Duedingen, Switzerland) according to instructions of the manufacturer. The test was performed in the laboratory of the University Children's Hospital in Basel and has been shown to be highly reliable [14]. In addition, serum samples that were indeterminate by ELISA were analysed by fluorescent-antibody staining of membrane antigen in VZV-infected cells (FAMA). The result as determined by FAMA was then used for further analyses.

FAMA was performed at the German National Reference Laboratory for VZV in Jena, Germany, according to standard procedures (available from authors upon request).

Statistics

Statistical analyses were performed with the SPSS 10.0.0 programme (SPSS Inc., Chicago, IL, USA). Positive predictive and negative predictive values were calculated for definite and negative histories of varicella. Furthermore, the positive predictive value was also calculated for "positive, probable, or possible" history of varicella and similarly, the negative predictive value was calculated for "negative or unknown" history of varicella.

Ethical review

The study protocol was approved by the ethics committee of the University of Basel Medical Faculty.

Results

Study population

Overall, 449 patients (210 females, 47%) were recruited. Mean age was 6.4 years and the median was 5.4 years. Specifically, 167 subjects were 1–4 years old (group 1), 136 were 5–8 years old (group 2) and 146 were 9–18 years old (group 3). In accordance with the overall distribution of nationalities of patients hospitalised in our institution, 264 (59%) subjects were Swiss and 185 (41%) had various other nationalities.

Varicella history and seroprevalence

Varicella history was definite in 234 (52%; 95% confidence interval, CI: 47–57), probable in 12 (3%; 95% CI: 1.2–4.2), possible in 1, negative in 196 (44%; 95% CI: 39–48) and unknown in 6 (1%; 95% CI: 0.3–2.4) study subjects. In groups 1, 2 and 3, the rates of a definite history of varicella were 24% (40 of 167; 95% CI: 17–30), 56% (76 of 136; 95% CI: 47–64), and 81% (118 of 146; 95% CI: 74–87), respectively.

VZV serum IgG antibodies were found in 274

Table 1

VZV-IgG antibody results* compared to personal history** by age groups.

	definite n pos/total (%)	probable n pos/total (%)	possible n pos/total (%)	negative n pos/total (%)	unknown n pos/total (%)	total n pos/total (%)
% = Positive predictive values						
1–4 years	37/40 (93)	1/2 (50)	0/0 (0)	4/124 (3)	0/1 (0)	42/167 (25)
5–8 years	76/76 (100)	3/4 (75)	1/1 (100)	12/53 (23)	1/2 (50)	93/136 (68)
9–18 years	116/118 (98)	6/6 (100)	0/0 (0)	14/19 (74)	3/3 (100)	139/146 (95)
Total	229/234 (98)	10/12 (83)	1/1 (100)	30/196 (15)	4/6 (67)	274/449 (61)
	definite n neg/total (%)	**probable n neg/total (%)**	**possible n neg/total (%)**	**negative n neg/total (%)**	**unknown n neg/total (%)**	**total n neg/total (%)**
% = Negative predictive values						
1–4 years	3/40 (7)	1/2 (50)	0/0 (0)	120/124 (97)	1/1 (100)	125/167 (75)
5–8 years	0/76 (0)	1/4 (25)	0/1 (0)	41/53 (77)	1/2 (50)	43/136 (32)
9–18 years	2/118 (2)	0/6 (0)	0/0 (0)	5/19 (26)	0/3 (0)	7/146 (5)
Total	5/234 (2)	2/12 (17)	0/1 (0)	166/196 (85)	2/6 (33)	175/449 (39)

* pos = positive, neg = negative

** in categories "definite", "probable", "possible", "negative", and "unknown"

(61%; 95% CI: 56–65) of 449 study subjects. Seroprevalence compared to history by age is shown in table 1. Seroprevalence was 25% (95% CI: 19–32), 68% (60–76) and 95% (92–99) in 1–4 year olds, 5–8 year olds, and 9–18 year olds, respectively.

The positive predictive value of a definite history of varicella was 98% (95% CI: 96–100) in the total study population and 93% (84–100), 100%, and 98% (96–100) for groups 1, 2, and 3, respectively (table 1). When the 13 patients with a probable or possible history were included, positive predictive values remained unchanged with 97% in the whole study population and 98% in group 3.

The negative predictive value of a negative varicella history was 85% (95% CI: 80–90) in the total study group. The values decreased with increasing age: group1: 97% (94–100); group 2: 77% (66–89); group 3: 26% (5–48). When the few patients with an unknown history were included (n = 6), the negative predictive values remained basically unchanged.

Discussion

In this study we found that seroprevalence of VZV antibodies increased by age and reached 95% in 9–18 year old children (table 1). This is in accordance with results from our previous, comprehensive Swiss seroprevalence study where 96.5% of 1709 11–17 year old adolescents were seropositive for VZV-IgG [14].

A positive varicella history was very reliable with positive predictive values greater than 93% regardless of patient age. Similarly, reliability of varicella history in Greek children was recently found to be 88% [8]. In contrast, negative predictive values in our study decreased from 97% in young children to 26% in older children and adolescents. For a presumptive immunization strategy in adolescents, the high positive predictive value is important in order to identify susceptible individuals. However, the comparatively low negative predictive value indicates that a substantial number of individuals would get immunized unnecessarily. Assuming that our findings are representative for the total Swiss pediatric population and that compliance with an immunization recommendation was 100%, presumptive immunization of older children and adolescents (9–18 years) with a negative or unknown varicella history would lead to the following scenario: 22 of 146 (15%) individuals of this age group would be eligible for immunization based on history, although only 5 (23%) of these 22 individuals lack VZV-IgG antibodies, which is 3.4% of the total in this age group. Therefore, with an estimated vaccine efficacy of 95% and a low number of false-positive histories, a selective immunization strategy targeted at individuals 9–18 years of age with a negative or unknown varicella history could increase seroprevalence in that age group from 95% to approximately 98.5%. This would reduce the burden of VZV infection in adolescence and adulthood significantly.

It has been argued that presumptive immunization is less cost-effective than identification of susceptible individuals by serotesting of older children and adolescents [7, 9, 15]. However, a significant number of adolescents may not return for immunization after susceptibility has been determined [15, 16]. Based on these considerations, a presumptive varicella immunization strategy for all adolescents 12 to 15 years of age with a negative history was introduced in Germany in 2000 and in Switzerland (11–15 years of age) in 2004 [13, 17]. Serological testing of those with an uncertain history before immunization is accepted as a valid alternative in Switzerland [13]. However, in our view this should only be considered on a carefully evaluated individual basis. This history based vaccination strategy for adolescents could serve as a model for other countries where a universal immunization programme is not feasible.

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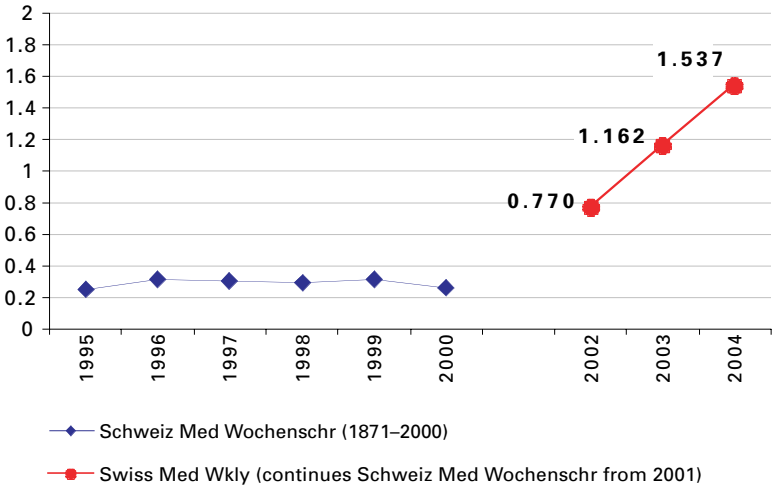

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