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BRIEF COMMUNICATION

# Reversal of Immunoglobulin A Deficiency in Children

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**Abstract**
*Purpose* Immunoglobulin A deficiency (IgAD) is the most common primary immunodeficiency in the general population. It is defined as a serum IgA level below or equal to 0.07 g/l with normal IgM and IgG levels in children over the age of 4. However, a few cases of reversal of IgAD at later ages have been observed previously, especially in pediatric patients. This study aimed at investigating the frequency of reversal in a large cohort of children and young adults in order to evaluate the present definition of IgAD.
*Methods* Clinical laboratory records from 654 pediatric IgA deficient patients, 4–13 years of age, were retrieved from five university hospitals in Sweden. Follow up in the children where IgA serum levels had been routinely measured was subsequently performed. In addition, follow up of the IgA-levels was also performed at 4, 8 and 16 years of age in children who were IgA deficient at the age of 4 years in a Swedish population-based birth cohort study in Stockholm (BAMSE).
*Results* Nine out of 39 (23.1 %) children who were identified as IgAD at 4 years of age subsequently increased their serum IgA level above 0.07 g/L. The average age of reversal was 9.53±2.91 years. In addition, 30 out of the 131 (22.9 %) children with serum IgAD when sampled between 5 and 9.99 years of age reversed their serum IgA level with time. The BAMSE follow up study showed a reversal of IgAD noted at 4 years of age in 8 out of 14 IgAD children at 16 years of age (5 at 8 years of age) where 4 were normalized their

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serum IgA levels while 4 still showed low serum levels of IgA, yet above the level defining IgAD. The results indicate that using 4 years of age, as a cut off for a diagnosis of IgAD may not be appropriate.

*Conclusions* Our findings suggest that a diagnosis of IgAD should not be made before the early teens using 0.07 g/L of IgA in serum as a cut off.

**Keywords** IgA deficiency · reversal · diagnostic definition

## Introduction

Immunoglobulin A deficiency (IgAD) is the most common human primary immunoglobulin deficiency in the general population and is defined as a serum level of IgA below or equal to 0.07 g/l in the presence of normal levels of other immunoglobulin isotypes in an individual older than 4 years of age [1, 2]. Partial IgAD refers to detectable (>0.07 g/l) but decreased IgA levels (more than 2 standard deviations below the normal age-adjusted means). The threshold of 4 years of age is used to prevent premature diagnosis of IgAD, which may be transient in children due to a delayed maturation of the immune system. IgAD is a lifelong disorder in most cases [3–6] and reports have shown that low IgA levels remain stable in IgAD patients during more than 20 years of observation [7]. However, several reports have documented cases of reversion of IgAD in pediatric patients diagnosed over the age of 4 [8–12]. This study was initiated in order to assess the frequency of reversal of IgAD so as to evaluate the validity of the present definition of IgAD.

## Materials and Methods

### Study Group

Six hundred fifty-four children, having been referred between 4 and 13 years of age for testing due to gastrointestinal symptoms, and identified with IgAD from laboratory data

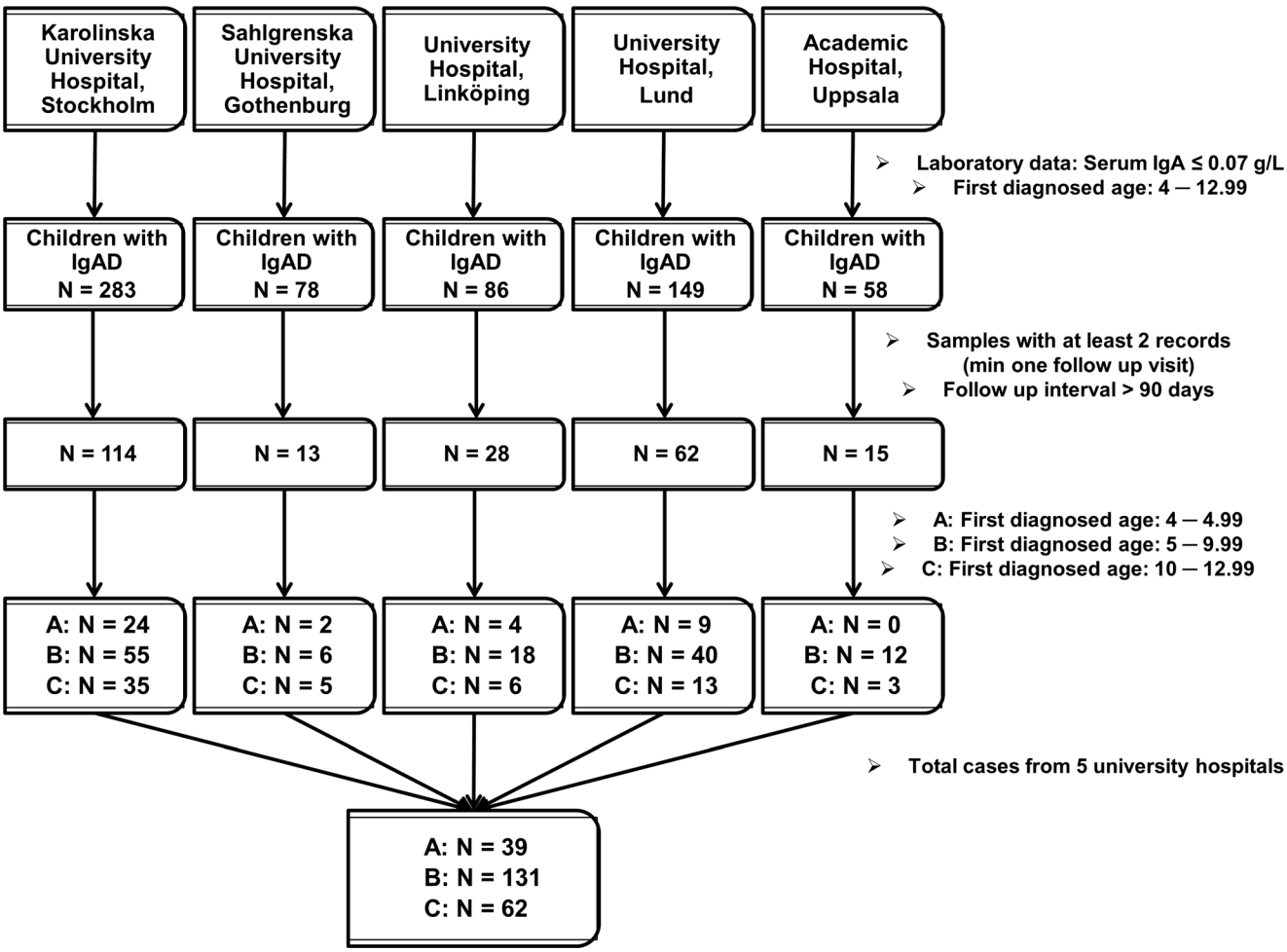


**Fig. 1** Flow chart describing the identification of children with IgAD. Flow chart showing children who remain IgAD and those who have increased their serum IgA level above 0.07 g/l (reverse)

were collected between 1992 and 2012 at five Swedish university hospitals (Karolinska hospital in Stockholm, Sahlgrenska hospital in Gothenburg, the University hospital in Lund, the University hospital in Linköping and the University hospital in Uppsala) and selected for follow up analysis. The follow up was performed by collecting data from patients with routinely collected multiple laboratory records with a minimum interval of 90 days. The age of IgAD reversal was defined at the date of first IgA value over 0.07 g/L or the first medical report indicating that IgA was observed. The follow up ended at 31 Jan 2014. Ethical approval was obtained from the Regional ethical review board in Stockholm.

### BAMSE Follow Up Study

During 1994–1996, all children born in a predefined area of Stockholm were invited to participate in a prospective study (the Children, Allergy, Milieu, Stockholm, Epidemiological survey [BAMSE]). The study design has been described previously [13]. In total, 14 IgAD children out of a cohort of 2423 were identified at the age of 4 [14] and the group has been subsequently followed up. All 14 children with IgAD had serum samples collected at the 16-year old follow up. However, only 10 of the 14 deficient children had serum samples available at the 8-year old follow up. The IgA levels of the follow up samples were determined using a sandwich ELISA as described previously [14]. Ethical approval was obtained from the Regional ethical review board in Stockholm.

### Statistical Analysis

All statistical analyses were performed using Microsoft Excel 2010 (Microsoft, Seattle, WA, USA) and GraphPad Prism software (GraphPad, San Diego, CA, USA). Fisher's exact test was used for evaluating non-parametric double group analysis and $p<0.05$ was regarded as significant.

## Results

Six hundred fifty-four children, 4–13 years of age, who were diagnosed with IgAD in 1992–2012 at the five participating university hospitals were identified (283 children from the Karolinska University hospital in Stockholm, 78 children from the Sahlgrenska University hospital in Gothenburg, 86 children from the University hospital in Linköping, 149 children from the University hospital in Lund and 58 children from the University hospital in Uppsala). Out of these, 232 had follow up (min interval 90 days) laboratory records up to 31 Jan 2014. In order to assess the validity of the current age of 4 years as a basis for diagnosis and suggest new potential cut off age, the children were subsequently divided into 3 age

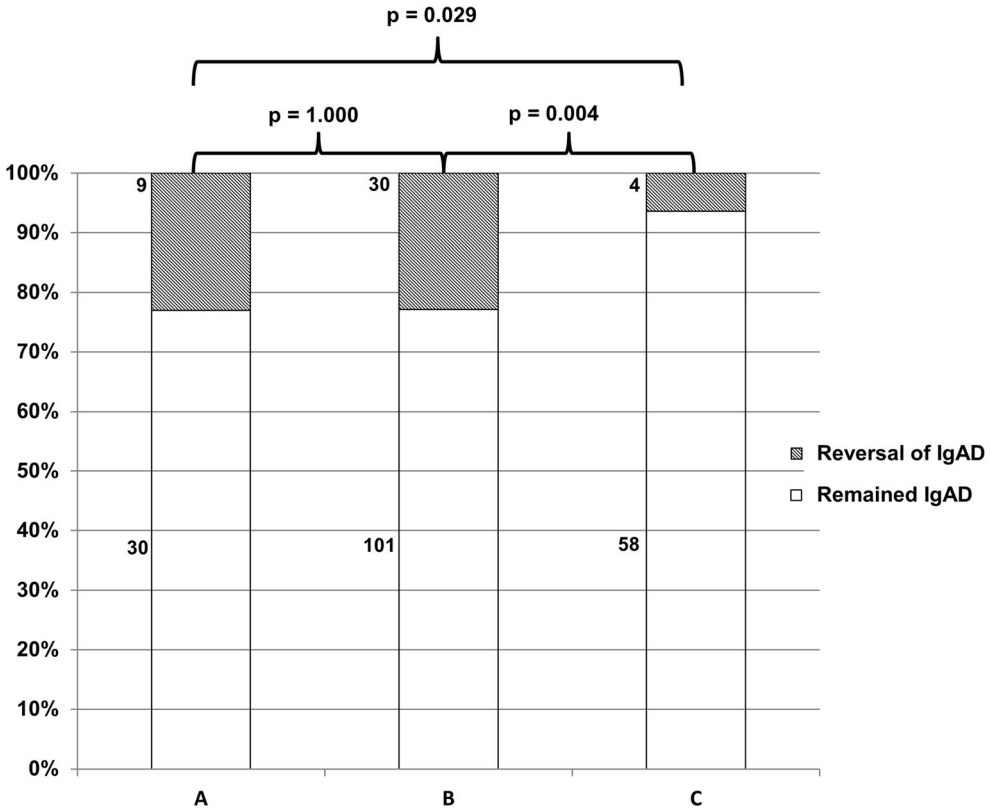


**Fig. 2** Reversal of IgAD in children with different diagnostics age group. *Group A*: IgAD diagnosed between 4 and 4.99 years of age. *Group B*: IgAD diagnosed between 5 and 9.99 years of age. *Group C*: IgAD diagnosed between 10 and 12.99 years of age. Fisher's exact test was used for comparing non-parametric double group analysis and $p<0.05$ was regarded as significant. Number of cases is shown in the figure

groups (A: 4–4.99; B: 5–9.99; C: 10–12.99) based on the age when they were first diagnosed with IgAD (Fig. 1).

### Reversal of IgAD in Children

As shown in Fig. 2, reversal of IgAD was observed in 23.1 % of the 39 children ($n$=9) who had been identified at 4 years of age (group A). The average age for the reversal was at 9.53± 2.91 years. Among these children, 4 were boys and 5 were girls. In group B, reversal of IgAD was seen in 30 out of 131 (22.9 %) children in group B whereas only 4 out of 62 (6.5 %) in group C, showed reversal of IgAD during the follow up period. The frequency of reversal in group A was significantly higher ($p$=0.029) as compared to group C and the difference in the rate of reversal of IgAD in group B was significantly higher as compared to group C ($p$=0.004). However, there were no significant differences in gender in the reversal of IgAD within the respective age at diagnosis (Supplemental Table 1).

### BAMSE Follow Up Study

Previous findings have shown that the level of IgA in serum from 5 out of the 10 tested IgAD children had increased their serum IgA levels at the 8-year old follow up [14]. All 14 serum IgA levels from the 16-year old follow up were analyzed using ELISA and 6 out of the 14 children remained IgA deficient while 8 children showed an increase in serum IgA levels above the deficient level. Out of the eight children, four children showed normal IgA levels, while four were partially deficient, giving a prevalence of IgAD in the BAMSE cohort of 1: 404 at 16 years of age (Supplemental Table 2).

## Discussion

There is hardly any diagnostic problem in adults using the present guidelines for IgAD. However, the diagnosis in children may be more complicated due to the delay in the development of the immune system. To date, several studies have shown that a proportion of pediatric IgAD cases maybe transient [8–12, 15]. Ostergaard et al. showed that normalization of IgA levels in 4 out of 6 deficient children even included children who had been identified as IgAD over the age of 4 [9]. Likewise, Shkalim et al. reported a girl who was diagnosed with IgAD at the age of 8 years who normalized her serum IgA level at 15.5 years [12]. Our study showed that around 23.1 % (9 out of 39) of the children that had been diagnosed as IgAD at 4 years of age increased their serum IgA level above 0.07 g/l at an average age of 9.53±2.91. In addition, 30 out of 131 (22.9 %) children with serum IgA levels ≤0.07 g/L between 5 and 9.99 year old increased their serum IgA beyond 0.07 g/L at average age at 12.21±3.43. A higher rate of reversal was found in these age groups as compared to the children who had been identified as IgAD beyond 10 years of age. In our retrospective study, a total of 39 out of 170 (22.9 %) children who were diagnosed as IgAD before 10 years of age increased their serum IgA level above the IgAD range with time. This observation indicates that more than one-fifth of the tested Swedish children may have a delay in the ontogeny of the immune system that affects serum IgA levels. It may thus be too early to diagnose IgAD by using 0.07 g/L as a cut off not only in children younger than four but also beyond that age.

The BAMSE follow up study showed that 57.1 % (8 out of 14) of the children had reversed their IgAD during a follow up period of 12 years. The percentage of reversal was higher as compared to children with suspected gastrointestinal diseases. The observation may be due to that the children from the BAMSE study represent a population-based cohort as compared to children who were suspected to have disease(s). Therefore, the reversal of the serum IgA level may potentially be higher in asymptomatic individuals.

In summary, our results indicate that the 4-year age limit for the diagnosis of IgA deficiency with 0.07 g/L as cutoff may need to be adjusted in order to prevent a premature diagnosis of IgAD. A definitive IgAD diagnosis should not be made before the early teens. The present findings may contribute to the development of more efficient diagnostic workup schemes for pediatric patients with a suspected IgAD.

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**Conflict of Interest** The authors declare that they have no conflict of interest.

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