ONLINE VERSION: ISSN 1028-4818

RPNS-1853

Multimed 2025; 29:e2974

Original article

Predictive factors for transient IgA deficiency

Predictive factors for transient IgA deficiency

Predictive factors for transient IgA deficiency

Reynel Marrón González I https://orcid.org/0000-0003-4840-5536

Lidia Cecilia Pérez Acevedo II* https://orcid.org/0000-0002-9477-399X

Maricarmen González-Costa III https://orcid.org/0000-0002-4202-5412

Misella Reyes Fajardo IV https://orcid.org/0000-0001-7210-2653

Barbara de la Caridad Addine Ramirez IV https://orcid.org/0000-0002-4203-8387

[Yo]Granma University of Medical Sciences. Carlos Manuel de Céspedes Provincial University Hospital. Outpatient Medical Center. Granma, Cuba.

[II]Center for Molecular Immunology. Havana, Cuba.

[III]Milanés Provincial Pediatric Teaching Hospital. Granma, Cuba.

[IV]Faculty of Medical Sciences of Bayamo. Granma, Cuba.

*Corresponding author:lidiacperez995@gmail.com

SUMMARY

Permanent or transient immunoglobulin A deficiency is the most common primary immunodeficiency. Knowledge of the factors associated with transient deficiency would allow for its prevention and improved diagnostic and therapeutic management. A case-

This work by Multimed is licensed under a https://creativecommons.org/licenses/by-nc-sa/4.0/

control study was conducted to identify predisposing factors for the development of transient IgA deficiency in Granma, in 78 patients (26 cases, 52 controls) seen in the Immunology clinic between 2012 and 2024. Clinical and epidemiological variables were evaluated using the odds ratio (OR-95% CI) and multivariate analysis with a logistic regression model. Univariate analysis revealed the following predisposing factors: birth by cesarean section, lack of breastfeeding, medication use, protein loss, presence of celiac disease, malnutrition, and dysbiosis; the latter was the variable with the most significant independent influence in the multivariate analysis (OR 9.55-95% CI, p=0.032). Dysbiosis, cesarean birth, and lack of breastfeeding were predisposing factors for suffering from transient IgA deficiency.

Keywords: Transient IgA deficiency; Secondary immunodeficiency; Predisposing factors; Dysbiosis.

SUMMARY

Permanent or transient immunoglobulin A deficiency is the most common primary immunodeficiency. Knowledge of factors associated with transient deficit would allow its prevention and better diagnosis and therapeutic management. A case-control study was conducted to identify predisposing factors for the development of transient IgA deficiency in Granma in 78 patients (26 cases, 52 controls) seen in the Immunology clinic between 2012 and 2024. Clinical and epidemiological variables were evaluated, using Odds Ratio (OR-CI 95%) and multivariate analysis with a logistic regression model. The univariate analysis showed the following predisposing factors: cesarean birth, absence of breastfeeding, medication consumption, protein loss, presence of celiac disease, malnutrition and presence of dysbiosis; the latter was the most important variable with independent influence in the multivariate analysis (OR 9.55-95% CI, p=0.032). Dysbiosis, cesarean birth, and lack of breastfeeding were predisposing factors for transient IgA deficiency.

This work by Multimed is licensed under a
https://creativecommons.org/licenses/by-nc-sa/4.0/

ONLINE VERSION: ISSN 1028-4818

RPNS-1853

Keywords: Transient IgA deficiency; Secondary immunodeficiency; Predisposing factors; Dysbiosis.

SUMMARY

A permanent or temporary deficiency of immunoglobulin A is the most common primary immunodeficiency. The knowledge of two factors associated with the transient deficit would allow its prevention and better diagnostic and therapeutic management. A case-control study was carried out to identify predisposing factors for the development of transient IgA deficiency in Granma in 78 patients (26 cases, 52 controls) treated at the Immunology clinic between 2012 and 2024. The clinical and epidemiological variations were evaluated, by means of Odds Ratio (OR-CI 95%) and multivariate analysis with logistic regression model. A univariate analysis showed the following predisposing factors: cesarean delivery, absence of maternal milk, medication consumption, protein loss, presence of celiac disease, malnutrition and presence of dysbiose; The latter was a more important variable with independent influence in the multivariate analysis (OR CI 9.55-95%, p=0.032). Dysbiose, cesarean delivery and lack of maternal breastfeeding are predisposing factors for transient IgA deficiency.

Keywords: Transient IgA deficiency; Secondary immunodeficiency; Predisposing factors; Disbiose.

Received: 5/10/2024

Approved: 02/20/2025

Introduction

Immunoglobulin A deficiency (IgAD) can go unnoticed, leading to false diagnoses and

This work by Multimed is licensed under a
https://creativecommons.org/licenses/by-nc-sa/4.0/

unexplained reactions to blood products. The current definition is defined as IgAD when serum IgA is less than 7 mg/dL for the total deficiency and 7–78 mg/dL for the partial deficiency, with normal serum concentrations of immunoglobulin isotypes IgM and IgG. It is diagnosed in children after 4 years of age and in adults in whom other causes of hypogammaglobulinemia have been excluded. (1)

The incidence of IgAD is 1 in 3000 in the general population, with a higher incidence in men. In Caucasians, the incidence is approximately 1 in 600, and is lower in Africans and Japanese. (1,2)

IgADI can be primary or transient, disappearing, or even secondary, developing after normal IgA levels have been established. In the 1960s, 1970s, and 1980s, the transient deficiency and the ages of reversal of low immunoglobulin A levels that appear in childhood were widely studied. The most accepted age for reversal of the transient deficiency is 4 years, (3) although some studies suggest 7 years and others suggest 10 years or early onset of adolescence. (4) The results of these investigations demonstrated that delayed maturation of IgA-producing systems occurs frequently.

In children with low IgA levels before the age assumed for possible reversal, healthcare professionals have no clear indications of whether the deficiency is temporary or will persist over time. The researchers, who are also clinical immunologists, believe that understanding the factors associated with non-permanent IgA deficiency would allow for its prevention, save scarce diagnostic resources, and aid in therapeutic decision-making. These factors motivated the present study, which aims to identify the predisposing factors for the development of temporary IgA deficiency in Granma.

Methods

An analytical case-control study was conducted at the Carlos Manuel de Céspedes Provincial Hospital in Bayamo, Granma, between 2012 and 2024. The sample consisted of

This work by Multimed is licensed under a
https://creativecommons.org/licenses/by-nc-sa/4.0/

patients who had received immunology care and whose medical records included the necessary data for the study. The sample consisted of 78 patients, divided into two groups.

ANDThe case group consisted of 26 patients with DIgA, diagnosedafter one year of age or before, who maintained this condition after 12 months, in which the deficit would have disappeared before the time of the study. For each patient diagnosed with IgAD, two patients who did not have this condition were paired, selected by simple random sampling among the members of the universe who had complete data (52 patients - control group).

Dependent variable: presence of IgA deficiency. In the case group, the age at which the deficiency disappeared was described.

Independent variables: Presence of dysbiosis, birth by cesarean section, absence of breastfeeding (BF), presence of celiac disease (CD), presence of protein losses, medication use(carbamazepine, steroids, phenytoin, valproic acid),and protein-energy malnutrition.

Data analysis was performed using SPSS 25. Absolute and relative frequencies were used. Univariate analyses were performed, evaluating: Odds Ratio (OR) with (95% CI) and a multivariate analysis with a logistic regression model.

The ethical principles of scientific research were complied with.

Results

Analysis of IgA levels in the 26 patients in the case group placed them in partial immunoglobulin deficiency.

Chart 1 shows the age at which IgA disappeared. IgA levels returned to normal at 4 years in 16 patients.

This work by Multimed is licensed under a
https://creativecommons.org/licenses/by-nc-sa/4.0/

ONLINE VERSION: ISSN 1028-4818

RPNS-1853

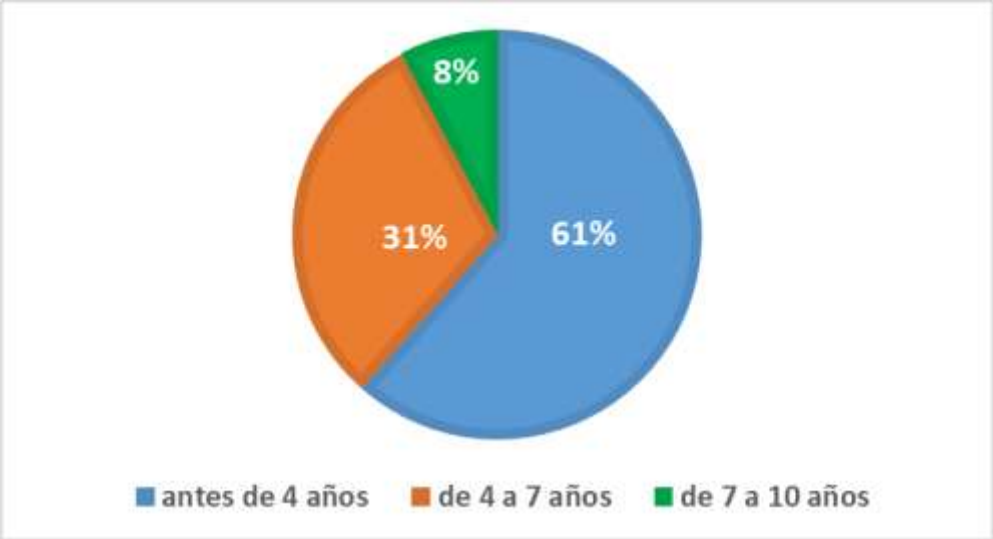

Chart 1. Distribution of patients with transient IgA deficiency according to age of disappearance.

Table 1 presents the results of the univariate statistical analysis. Dysbiosis was reported in 84.61% of patients with immunodeficiency and in 21.15% of immunocompetent patients. Cesarean delivery occurred in 76.92% of cases and 15.38% of controls. Malnutrition was present in 65.38% of patients with transient IgA deficiency. 61.53% of patients with immunodeficiency did not receive breast milk, and 13.46% of controls did not. In all cases, the factors were statistically significantly associated with transient IgA deficiency.

Table 1. Univariate analysis. Modifiable factors predisposing to transient IgA deficiency.

Modifiable factors		Cases (26)		Controls (52)		Total (78)		OR	P
		Neither	%	No	%	No	%		
Caesarean birth	Yeah	20	76.92	8	15.38	28	35.89	14.93	0.000
	No	6	23.07	44	84.61	50	64.10		
Absence of breastfeeding	Yeah	16	61.53	7	13.46	23	29.48	9,075	0.000
	No	10	38.46	45	86.53	55	70.51		
Presence of dysbiosis	Yeah	22	84.61	11	21.15	43	55.12	17,18	0.000
	No	4	15.38	41	78.84	45	57.69		
Medication use	Yea	12	46.15	3	5.76	15	19.23	16.20	0.000

This work by Multimed is licensed under a
https://creativecommons.org/licenses/by-nc-sa/4.0/

	h								
	No	14	53.84	49	94.23	63	80.76		
Malnutrition	Yea h	17	65.38	4	7.69	21	26.92	10.24	0.000
	No	9	34.61	48	92.30	57	73.03		

Source: Medical records

The presence of celiac disease (CD) was significantly associated with transient IgA deficiency (OR 8.30; p 0.007), as was the presence of protein-losing diseases (OR 13.21; p 0.006). Univariate analysis of both non-modifiable factors is shown in Table 2.

Table 2. Univariate analysis. Non-modifiable factors predisposing to transient IgA deficiency.

Non-modifiable factors		Cases (26)		Controls (52)		Total (78)		OR	P
		No	%	No	%	No	%		
Protein-losing diseases	Yea h	6	23.07	2	3.84	8	10.25	13.21	0.006
	No	20	76.92	50	96.15	70	89.74		
Presence of celiac disease	Yea h	9	34.61	3	5.76	12	15.38	8,300	0.007
	No	17	65.38	49	94.23	66	84.61		

Source: Medical records

Table 3 presents the results of the binary logistic regression analysis. It was shown that the presence of dysbiosis was the factor with the greatest independent influence on the development of transient IgA deficiency, increasing the risk 11-fold (OR 11.917; 95% CI; p=0.011). Medication use remained significant (OR 8.68; 95% CI; p=0.047). The remaining factors were not significantly relevant.

Table 3. Multivariate analysis. Result of the model fit with the variablesschosen.

Factors	Exp B	P	IC	
			Lower	superior
Birth by cesarean section	2,920	0.392	0.251	33,907
Absence of breastfeeding	0.253	0.310	0.018	3,579

This work by Multimed is licensed under a
https://creativecommons.org/licenses/by-nc-sa/4.0/

Presence of Dysbiosis	11,917	0.011	1,745	81,374
Medication use	8,687	0.047	1,026	73,517

Discussion

IgAD is associated with disorders in T reg cells, HLA genes, and the methylation status of some genes. These arguments link the deficit in question to modifiable epigenetic disorders, thus serving as a basis for actions that affect environmental factors and explain the possible reversal. (5)

In the present investigation, all cases with transient IgA deficiency were partial. These results coincide with those of Plebani A, who studied 80 children with selective IgA deficiency. Fifty percent of the partial deficiencies reached normal IgA levels by around 14 years of age. No individual with total deficiency reverted. It was concluded that in childhood, partial deficiency is frequently transient. (6)

The age of IgAD reversal was not homogeneous, some resolved around 4 years of age, but some did so between 4 and 7 years of age, and others at ages older than 7 years. This is in agreement with Lim CK et al., who studied 654 patients and found variability between the ages of IgAD resolution. They suggest that the age of 10 years or early adolescence should be assumed. (4) A study carried out in Poland in 2020 assumes 4 years of age as the diagnostic age for transient IgAD, considering it the most frequent age for reversal. (3) In the study carried out by Nurkic J, of a total of 91 patients with low IgA levels, reversal occurred in 77 cases around 7 years of age. (5)

IgAD is associated with HLA-DQB1*O2 which is also a predisposing factor for developing celiac disease, this partly explains the frequency with which both diseases coexist. (7) The finding of elevated IL-12 secretion in patients with IgAD supports the prevalence of Th 1 pattern. (8) This brings with it a decrease in Th2 and can lead to IgA deficiency due to a decrease in Il-5. (6) Vosughimotlagh et al., in a meta-analysis that included 40 studies on

This work by Multimed is licensed under a
https://creativecommons.org/licenses/by-nc-sa/4.0/

IgA deficiency, reported a cumulative prevalence of celiac disease in 6.57% and 6.66% of cases with total and partial IgAD, respectively. (9) The present study shows higher levels of association. Swain reported a significantly higher proportion of patients with CD and IgAID compared with individuals with normal IgA levels (67% vs 23%, P = 0.03, and 29% vs 12%, P = 0.0081). (10)

IgAD can be acquired as a result of the use of medications such as phenytoin, carbamazepine, valproic acid, gold salts, penicillamine, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs. The explanation is particular considering the mechanisms of action of each drug. Matsuda found that, of 78 patients with transient IgAD, 33 (42.30%) were associated with medication use. (11) These results are similar to those obtained in the present study.

Intestinal homeostasis is influenced by both mucosal and serum IgA, and its decrease affects the microbiota. Dysbiosis leads to the absence or decrease of organized follicles in the colon and/or to the poor development of Peyer's patches in the intestine and therefore decreases IgA production, (12) establishing a harmful cycle for homeostasis. A mature and well-proportioned microbiota is capable of reducing IL-10 production and this is essential for the adequate generation of IgA. (13,14)

A 2019 study measured the presence of microbiota in feces and described a decrease in microbiota diversity in patients with IgAD (measured as alpha diversity). The study conducted by the group of authors was limited to measuring the presence or absence of dysbiosis, that is, the predominance of bacteria according to Gram-negative classification.. (15) It is described that the decrease in IgA does not affect the alpha diversity of the microbiota, however the decrease or change in the microbiota, via affecting the formation of Peyer's patches, does affect the production of IgA, both mucosal and serum. (13)

In general terms, BF, vaginal birth, and a healthy early childhood contribute to the establishment of the initial microbiota. (16) From this previously established relationship, it follows that the justification for the influence of BF and cesarean birth on IgAD is based

This work by Multimed is licensed under a
https://creativecommons.org/licenses/by-nc-sa/4.0/

on the impact that both factors have on the correct establishment of the microbiota. In 2020, Galazzo et al. demonstrated that the composition of the early microbiota of infants is strongly affected by the delivery route until week 13 after birth. It was also shown that at 31 weeks, those born vaginally maintained a significantly greater diversity of the microbiota, with higher levels of Bacteroidetes, than those born by cesarean section, regardless of the type of breastfeeding received. (16) This suggests that the positive influence described for BF in the establishment of the microbiota does not compensate for the impact of cesarean birth.

In Cuba, in a study of malnourished patients, 63.06% of those studied presented decreased levels of IgA. (17) Recent studies have shown the importance of additional environmental factors such as vitamin A in IgA synthesis. It was described that concurrent deficiency of zinc and vitamin A suppresses the production of serum IgA and, to a lesser extent, mucosal IgA. They recognize that nutritional disorders were associated with DIgA but demonstrated this with statistical significance in the case of the measurement of these two elements. (12)

Protein loss leads to a decrease in essential amino acids, which negatively influences immunoglobulin synthesis. In the aforementioned study, Matsuda et al. found protein loss among the associated factors in 10 patients, representing 12.82%. (11) These results are lower than those reported by the authors in this article.

Conclusions

Dysbiosis, malnutrition, medication use, cesarean birth, and lack of breastfeeding have been identified as predisposing factors for transient IgA deficiency, with dysbiosis and medication use being the predominant influences.

This work by Multimed is licensed under a
https://creativecommons.org/licenses/by-nc-sa/4.0/

ONLINE VERSION: ISSN 1028-4818

RPNS-1853

Bibliographic references

1. Morawska I, Kurkowska S, Bębnowska D, Hrynkiewicz R, Becht R. The Epidemiology and Clinical Presentations of Atopic Diseases in Selective IgA Deficiency. J Clin Med. 2021; 10(17):3809.

2. Méndez Loayza D. de Á, Arriola Spátola MA, Gonzáles de Campos AL, Montenegro Pucci C, Olano Gossweiler C. Prevalence and characteristics of selective IgA deficiency in celiac patients. Rev Gastroenterol Peru. 2021 ;41(1):11-5.

3. Tąpolska-Jóźwiak K, Szczawińska-Popłonyk A. Selective IgA deficiency – does partial mean negligible? Pediatrics Polska - Polish J. Paediatrics. 2020; 95(1):1-5.

4. Lim CK, Dahle C, Elvin K, Andersson BA, Rönnelid J, Melén E, Bergström A. Reversal of Immunoglobulin A Deficiency in Children. J Clin Immunol. 2015; 35(1):87-91.

5. Nurkic J, Numanovic F, Arnautalic L, Tihic N, Halilovic D, Jahic M. Diagnostic Significance of Reduced IgA in Children. Med Arch. 2015;69(4):236-9.

6. Plebani A, Ugazio AG, Monafo V, Burgio GR. Clinical heterogeneity and reversibility of selective immunoglobulin A deficiency in 80 children. Lancet. 1986; 1(8485):829-31.

7. Poddighe D, Capittini C. The Role of HLA in the Association between IgA Deficiency and Celiac Disease. Dis Markers. 2021; 2021:8632861.

8. Ernest Andersen MC, Sander SD, Madsen G, Lillevang ST, Murray J, Husby S. Pediatric Celiac Disease and Selective IgA Deficiency: Unexpected Sequence of Events. J Clin Immunol. 2022; 42(6):1342-1346.

9. Vosughimotlagh A, Rasouli SE, Rafiemanesh H, Safarirad M, Sharifinejad N, Madanipour A, et al.Clinical manifestation for immunoglobulin A deficiency: a systematic review and meta-analysis. Allergy Asthma Clin Immunol. 2023; 19(1):75

10. Swain S, Selmi C, Gershwin ME, Teuber SS. The clinical implications of selective IgA deficiency. J Transl Autoimmun. 2019; 2:100025.

11. Matsuda KM, Arioka H, Kobayashi D. Risk factors of partial IgA deficiency among low serum IgA patients: a retrospective observational study. Cent Eur J Immunol. 2020;

This work by Multimed is licensed under a
https://creativecommons.org/licenses/by-nc-sa/4.0/

45(2):189-94.

12. Abokor AA, McDaniel GH, Golonka RM, Campbell C, Brahmandam S, Yeoh BS, et al. Immunoglobulin A, an Active Liaison for Host-Microbiota Homeostasis. Microorganisms; 9(10):2117.

13. Galant-Swafford J. Selective Immunoglobulin A Deficiency and the Microbiome. Crit Rev Immunol. 2021; 41(6):1-12.

14. Guo J, Ren C, Han X, Huang W, You Y, Zhan J. Role of IgA in the early-life establishment of the gut microbiota and immunity: Implications for constructing a healthy start. Gut Microbes. 2021; 13(1):1-21.

15. Catanzaro JR, Strauss JD, Bielecka A, Porto AF, Lobo FM, Urban A, et al. IgA-deficient humans exhibit gut microbiota dysbiosis despite secretion of compensatory IgM. Sci Rep. 2019; 9(1):13574.

16.Galazzo G, van Best N, Bervoets L, Dapaah IO, Savelkoul PH, Hornef MW, et al. Development of the Microbiota and Associations With Birth Mode, Diet, and Atopic Disorders in a Longitudinal Analysis of Stool Samples, Collected From Infancy Through Early Childhood. Gastroenterology. 2020; 158(6):1584-96.

17. Crespo Venega M, Montejil Rogers I, Mirabal Sánchez H, Carbonell Montiel Y, Abreu Rivero Y, Leal Yanes J. Immune system disorders in children under five years of age with protein-calorie malnutrition. Mediciego. 2022; 28(1):e2975.

Conflict of interest

The authors declare no conflicts of interest.

Authorship contribution

Conceptualization Ideas:Barbara de la Caridad Addine Ramirez, Reynel Marron Gonzalez.

Investigation: Lidia Cecilia Pérez Acevedo, Maricarmen González Costa.

This work by Multimed is licensed under a
https://creativecommons.org/licenses/by-nc-sa/4.0/

Methodology:Barbara de la Caridad Addine Ramirez, Reynel Marron Gonzalez.

Writing – original draft:Reynel Marrón González, Bárbara de la Caridad Addine Ramírez.

Writing – review and editing:Lidia Cecilia Pérez Acevedo, Maricarmen González Costa, Misella Reyes Fajardo.

I, Reynel Marrón González, on behalf of all the co-authors, declare the veracity of the content of the article Predictive factors for transient IgA deficiency.

This work by Multimed is licensed under a
https://creativecommons.org/licenses/by-nc-sa/4.0/