

PANDAS: Baseline Immunoglobulin Levels Predict Achievement of Remission at One Year Following IVIg Therapy

David S. Younger^{1,2*}, Phyllis A. Mast³ and Denis A. Bouboulis⁴

¹Department of Neurology, New York University School of Medicine, New York, NY, USA

²Division of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

³Innovative Research Associates, Inc, Sharon Hill, PA, USA

⁴Advanced Allergy, Immunology and Asthma, PC, Stamford, CT, USA

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*Corresponding author: David S. Younger, 333 East 34th Street, 1J, New York NY 10016, USA; E-mail: david.younger@nyumc.org.

Abstract

Introduction: In children and adolescents, a syndrome of exacerbations of tics and obsessive symptoms may occur after infection with group A beta-hemolytic streptococci. The syndrome is known as pediatric autoimmune neuropsychiatric disorder associated with group A beta hemolytic streptococcal infection (PANDAS). The literature suggests that IVIg therapy benefits some children diagnosed with PANDAS; however, no studies have focused on predictors of the beneficial effect.

Study Aims: To study baseline humoral immunity as a predictor of response to IVIg therapy.

Methods: Children in a single pediatrician's practice were screened clinically and by laboratory studies to establish the diagnosis of PANDAS and baseline Ig status. Those who met the diagnostic criteria received IVIg therapy every eight weeks for up to a year, examined at one month and one year following treatment, and scored for degree of improvement. Children with low Ig levels and those with normal or high levels at baseline were compared with respect to baseline demographic and clinical factors and one year outcomes. The outcome scores were dichotomized as improved (100 % improved) or not improved (< 100 % improved). The statistical significance of differences between groups was evaluated with chi-squared or Fisher's exact tests for categorical variables or t-tests for normally distributed continuous variables.

Results: In the cohort of 114 children (74 male, 40 female) with confirmed PANDAS, mean age was 10.57 years, and mean duration of symptoms of PANDAS 4.27 years. Baseline serum Ig levels were normal in 47.44 % and low in any category in 52.56 %. Serum IgG subclasses were low in 26.47 %, total IgG in 25.51 %, IgM in 16.28 %, and IgA in 10.48 %. Low levels of IgA ($p < 0.006$), IgG ($p < 0.0001$) and IgG subclasses ($p < 0.0003$) were associated with 100% improvement at 12 months. Of 114 patients, 22 (19.3 %) patients achieved 100 % improvement, all with low Ig levels, 20 of whom had low total Ig levels alone or in association with IgG subclass, IgA, or IgM levels. The remaining two patients had low IgG subclass levels alone or in association with low IgA. Age, sex, duration of disease, and baseline IgM levels were not associated with IVIg efficacy. Mild adverse effects of treatment occurred in 16% of the children.

Conclusions: Children with PANDAS who had baseline low IgA, IgG or IgG subclass levels were more likely than others to achieve 100 % improvement after IVIg therapy at 12 months follow-up.

Keywords: PANDAS; IVIg Therapy

of relative symptom quiescence and noted that in some patients, exacerbations were associated with group A beta-hemolytic streptococcal (GABHS) infections.

In 1998, Swedo and colleagues [4] described the clinical neuropsychiatric clinical and laboratory features of 50 children, all of whom met the criteria of prepubertal onset of OCD, motor tic disorders, episodic course, and association with GABHS infections. Children with known rheumatic fever, or overt chorea by history and physical examination leading to suspicion of Sydenham Chorea (SC), a known variant of rheumatic fever requiring antibiotic prophylaxis against GABHS, were excluded from the sample. The study found a striking association of the abrupt onset of OCD, tics and comorbid psychiatric symptoms with documented GABHS infection and increase in anti-streptococcal titers. The authors [4] postulated that the pathogenesis of PANDAS, like that of rheumatic fever, was due to exposure of a genetically and developmentally susceptible host to GABHS infection, which evoked an autoimmune response in the central nervous system (CNS) preferentially affecting extrapyramidal neurons of the basal ganglia.

The understanding of PANDAS has progressed since that report more than fifteen years ago [4-8]. The literature suggests that immune modulatory therapy, particularly intravenous immunoglobulin (IVIg), benefits some children diagnosed with PANDAS [9,10]. However no studies have focused on predictors of the beneficial effects. One possible predictor is baseline immunity. It is hypothesized that among children with PANDAS, those with low serum IgG levels at baseline will be more likely to recover following IVIg treatment than will children with normal serum IgG levels at baseline. To date, no studies have examined this relationship. An earlier unpublished manuscript authored by Younger [11] was submitted to the Epidemiology Department of the Mailman School of Public Health, Columbia University.

Methods

Data Sources

The patient database of Advanced Allergy Immunology and Asthma, PC, a primary care, pediatric office practice in Darien, Connecticut (CT), was screened to identify new patients clinically diagnosed with PANDAS between 2009 and 2014. Among 136 patients clinically diagnosed with PANDAS, 22 had the concomitant diagnosis of autism spectrum disorder and were excluded, leaving 114 patients, who comprised the study cohort. Names, addresses and other personal identifiers were removed from the medical records of all 114 patients in the study database their prior to analysis. The study was approved by the Institutional Review Board of Columbia University, New York (Protocol IRB-AAAQ7471 [MoY1]).

Introduction

From 1989 to 1992, Swedo and investigators in the Children Psychiatry Branch of the National Institute of Mental Health (NIMH) in Bethesda, Maryland [1-3] described the long-term courses of children and adolescents with Obsessive-Compulsive Disorders (OCD). The team identified a subgroup characterized by dramatic and acute symptom exacerbations interspersed with long periods

Study Population

The study population consisted of 114 patients first seen between 2009 and 2014 who met the criteria for PANDAS according to Swedo and colleagues [4] and in keeping with the National Institute of Mental Health (NIMH) (<http://www.nimh.nih.gov/health/publications/pandas/index.shtml>)

Criteria: Symptom onset between 3 years of age and puberty; episodic course of symptom severity; association with group A beta-hemolytic streptococcal infection (as documented by positive throat culture for streptococcus); association with neurological abnormalities that included physical hyperactivity or motor tics beyond the child's control; and abrupt onset or worsening of symptoms. All 114 patients had evidence of increased serum anti-streptolysin or anti-DNase B antibodies supporting a preceding streptococcal infection. The standard dosing regimen for IVIg was 1.5 grams per kilogram (g/kg) for two days every eight weeks; however, the duration of therapy was individualized based upon the anticipated need and the development of intolerable side effects. All IVIg adverse effects (AE) were recorded. Comorbid conditions were also recorded.

Outcome

The primary outcome of treatment was scored 1- 6 reflecting the clinician-assessed improvement recorded in the chart notes as the percentage of improvement at 1 month and 12 months follow up in response to IVIg treatment: 1, worse; 2, same; 3, 25% improved; 4, 50% improved; 5, 75% improved; and 6, 100% improved. The therapeutic efficacy of IVIg was defined as achievement of normality after a course of IVIg therapy at the 12-month follow-up.

Predictors

The exposures of interest were:

- Baseline total IgA, IgM, and IgG and IgG subclasses, measured in mg per deciliter (mg/dL). Because cutoff values for measured serum Ig's varied across labs, the measured value was referred to the individual laboratory's range of normality. For the purpose of this analysis, values were dichotomized as below or above the minimum in each range.
- Duration of IVIg therapy measured in months from the onset to the end of treatment. IVIg therapy was generally continued without significant delay, interruption or suspension.

Statistical Methods

Descriptive analysis was applied for all variables. Bivariate analyses with Chi-square and Fisher exact tests were employed to test the significance of the associations between baseline IgG status and the categorical distribution of other baseline demographic and clinical characteristics of the patients and between outcomes of interest and baseline demographic and clinical characteristics. T-test analyses for normally distributed continuous variable were used to test the association between treatment efficacy based upon attaining 100 % improvement and numerical risk factors. Detailed statistical analysis was performed using SAS 9.3 using a two-sided p-value < 0.05 for statistical significance.

Results

The mean overall age of the 114 children was 10.57 years (4 - 18 years); 71 % were older than 12 years of age, and 65 % were male. Baseline serum Ig levels were normal in 37 (47.44 %) and low in any category in 41 (52.56 %). We observed low levels of serum IgG

subclasses alone in 27 (26.47 %), total IgG in 25 (25.51 %), IgM in 14 (16.28 %) and IgA in 11 (10.48 %). The mean duration of symptoms of PANDAS was 4.27 years (1-12 years). Overall, the mean duration of IVIg treatment was 15.74 months (0.03 - 61.79 months). Fifty-one children (13 %) were on stable doses of serotonin reuptake inhibitors, α -adrenergic agonists, benzodiazepines, antipsychotics, or neuroleptics for concomitant stable neuropsychiatric disorders. Co-morbid conditions were noted in 26 (13 %), including serologic evidence of preceding Lyme exposure without active disease in 7 (6 %), asthma in 6 (5.2 %), and eczema and gastroesophageal reflux in 3 children each (2.6 %). The mean duration of IVIg treatment in the cohort was 15.74 months (0.03- 61.79). Two forms of IVIg therapy were used: Gamma Gard (69 %), Octagam (12 %) and both (18 %) (Table 1).

The results of bivariate analyses of the demographic and clinical characteristics of children with PANDAS by baseline IgG status are shown in Table 2. Older age, low IgA levels, and low IgG subclass levels were associated with low baseline IgG levels. The results of bivariate analyses of baseline Ig levels and IVIg treatment efficacy are shown in Table 3. Low baseline levels of IgA ($p < 0.006$), IgG ($p < 0.0001$) and IgG subclasses ($p < 0.0003$) were all significantly associated with IVIg efficacy in achieving 100 % improvement at 12 months. Gender, duration of disease, and baseline IgM levels were not significantly associated with IVIg efficacy. Of 114 patients, 22 (19.3%) patients achieved 100 % improvement, all with low Ig levels, 20 of whom had low total IgG levels alone or in association with IgG subclass, IgA, or IgM levels. The remaining two patients had low IgG subclass levels alone or in association with low IgA.

IVIg therapy was generally well-tolerated in this study cohort. Of a total of 1701 IVIg infusions, there were 348 AE (16%) which were overall mild in severity. They included 173 (10.2%) cases of headache followed by nausea in 53 (3.1%), vomiting in 41 (2.4%), other systemic symptoms in 32 (1.9%), and migraine in 24 (1.4%) cases. None of the children who had an AE required hospitalization. The AE were transient in nature, and most were relieved with acetaminophen, prednisone, and other prescribed medications, including migraine medications.

Variable	
AE	Y: has adverse effect during treatment; N: no adverse effect during treatment
Age	age at diagnosis, years
Dur_12	Y: duration of treat past 12 months; N: duration of treatment within 12 months
Duration of treatment	duration of IVIg treatment, months
Duration of PANDAS	duration of PANDAS before treatment, years
Efficacy-1year	Improvement at 12 months visit. 1, worse; 2, same; 3, 25% improved; 4, 50% improved; 5, 75% improved; and 6, 100% improved.
Efficacy	Therapeutic efficacy of IVIg. 1: achieved normality; 0: not achieved normality
Gender	Female or male
IgA	IgA level before treatment. L: low level; N: normal or high level
IgM	IgM level before treatment. L: low level; N: normal or high level
IgG	IgG level before treatment. L: low level; N: normal or high level
IgG_subs	IgG subclass levels before treatment. L: low level; N: normal or high level
PC_number	patient id
Weight_kg	weight of patient in kilogram

Table 1: Coding of Variables

Variables	Baseline IgG status								P-value
	Low		Normal		Missing		Total		
	N	%	N	%	N	%	N	%	
Total	25	21.9	73	64.0	16	14.0	114	100.0	
Age									0.02
3-10	9	36.0	45	61.6	8	50.0	62	54.4	
11-20	16	64.0	28	38.4	8	50.0	52	45.6	
Gender									0.19
Male	19	76.0	45	61.6	10	62.5	74	64.9	
Female	6	24.0	28	38.4	6	37.5	40	35.1	
Years since diagnosis									0.16
0-4	9	36.0	41	56.2	8	50.0	58	50.9	
5-	9	36.0	19	26.0	6	37.5	34	29.8	
Missing	7	28.0	13	17.8	2	12.5	22	19.3	
Duration of treatment									0.64
<12 months	12	48.0	39	53.4	5	31.3	56	49.1	
≥12 months	13	52.0	34	46.6	11	68.8	58	50.9	
Adverse effect									0.71
Yes	18	72.0	49	67.1	9	56.3	76	66.7	
No	7	28.0	23	31.5	7	43.8	37	32.5	
Missing	0	0.0	1	1.4	0	0.0	1	0.9	
Weight									0.42
≤40 kg	11	44.0	39	53.4	8	50.0	58	50.9	
>40 kg	14	56.0	34	46.6	8	50.0	56	49.1	
IgA									0.03
Low	6	24.0	5	6.8	0	0.0	11	9.6	
Normal	19	76.0	66	90.4	9	56.3	94	82.5	
Missing	0	0.0	2	2.7	7	43.8	9	7.9	
IgM									0.31
Low	5	20.0	9	12.3	0	0.0	14	12.3	
Normal	15	60.0	53	72.6	4	25.0	72	63.2	
Missing	5	20.0	11	15.1	12	75.0	28	24.6	
IgG subclass									0.0008
Low	13	52.0	13	17.8	1	6.3	27	23.7	
Normal	11	44.0	57	78.1	7	43.8	75	65.8	
Missing	1	4.0	3	4.1	8	50.0	12	10.5	
Treatment efficacy									<0.0001
100%	20	80.0	2	2.7	0	0.0	22	19.3	
<100%	4	16.0	69	94.5	0	0.0	73	64.0	
Missing	1	4.0	2	2.7	16	100.0	19	16.7	

Table 2: Demographic and clinical characteristics of children with PANDAS by baseline IgG status.

Discussion

We found that low serum baseline levels of IgG ($p < 0.0001$) and IgG subclasses ($p < 0.0003$) and IgA ($p < 0.006$) were associated with 100 % improvement in symptoms of PANDAS at 12 months follow-up. Older age, low IgA levels, and low IgG subclass levels were associated with low baseline IgG levels.

The inclusion criteria for PANDAS we used in our study have been used in other systematic research on the phenomenology of the symptoms of PANDAS and the use of immune modulatory therapy including IVIg for affected children [11]. We hypothesize that in some children the pathophysiology of PANDAS begins with a GABHS infection that stimulates the production of antibodies to GAS that cross-react and interact with neurons of the basal ganglia in the brain. Although a dysimmune response involving both humoral and cellular mechanisms preceding GABHS has generally been acknowledged in the literature [13-16], there is still uncertainty as to the correct management of affected children, particularly those with pervasive symptoms.

Although the treating physician administered the same therapy to all the children in his practice who met the criteria for PANDAS and tested their baseline immune function, he had not suspected that selective IgG, IgG subclass and IgA deficiencies would be associated with the efficacy of IVIg therapy.

The finding of selective humoral deficiencies in children with the most favorable outcome, namely full improvement, should be treated with caution. It does not link the disorder itself to humoral deficiency and it does not provide evidence regarding the optimal dose or duration of therapy. It also does not provide evidence that children's Ig deficiencies may have increased their susceptibility to repeat GABHS or that repeat GABHS may have contributed to the development of PANDAS symptoms. However, in this small sample from a single pediatric practice, by comparing children with and without Ig deficiencies, we identified a particular subgroup of children with PANDAS who responded favorably to IVIg.

A prior report [17] showed no differences in the levels of

Variables		IVIg treatment efficacy at 12 months								P-value
		100%		<100%		Missing		Total		
		N	%	N	%	N	%	N	%	
Total		22	19.3	89	78.1	3	2.6	114	100.0	
Age										0.01
	3-10	7	31.8	54	60.7	1	33.3	62	54.4	
	11-20	15	68.2	35	39.3	2	66.7	52	45.6	
Gender										0.15
	Male	17	77.3	54	60.7	3	100.0	74	64.9	
	Female	5	22.7	35	39.3	0	0.0	40	35.1	
Years since diagnosis										0.52
	0-4	9	40.9	48	53.9	1	33.3	58	50.9	
	5-	7	31.8	26	29.2	1	33.3	34	29.8	
	Missing	6	27.3	15	16.9	1	33.3	22	19.3	
Duration of treatment										0.89
	<12 months	11	50.0	43	48.3	2	66.7	56	49.1	
	≥12 months	11	50.0	46	51.7	1	33.3	58	50.9	
Adverse effect										0.66
	Yes	14	63.6	61	68.5	1	33.3	76	66.7	
	No	8	36.4	28	31.5	1	33.3	37	32.5	
	Missing	0	0.0	0	0.0	1	33.3	1	0.9	
Weight										0.27
	≤40 kg	9	40.9	48	53.9	1	33.3	58	50.9	
	>40 kg	13	59.1	41	46.1	2	66.7	56	49.1	
IgA										0.006
	Low	6	27.3	4	4.5	1	33.3	11	9.6	
	Normal	16	72.7	76	85.4	2	66.7	94	82.5	
	Missing	0	0.0	9	10.1	0	0.0	9	7.9	
IgM										0.32
	Low	4	18.2	9	10.1	1	33.3	14	12.3	
	Normal	13	59.1	57	64.0	2	66.7	72	63.2	
	Missing	5	22.7	23	25.8	0	0.0	28	24.6	
IgG										<0.0001
	Low	20	90.9	4	4.5	1	33.3	25	21.9	
	Normal	2	9.1	69	77.5	2	66.7	73	64.0	
	Missing	0	0.0	16	18.0	0	0.0	16	14.0	
IgG subclass										0.0003
	Low	12	54.5	14	15.7	1	33.3	27	23.7	
	Normal	9	40.9	64	71.9	2	66.7	75	65.8	
	Missing	1	4.5	11	12.4	0	0.0	12	10.5	

Table 3: Demographic and clinical characteristics of children with PANDAS by IVIg treatment outcome.

IgG and IgM between a cohort of 24 children with tics and OCD and age- and sex-matched controls, but significantly lower levels of total IgA in the patients ($*p = 0.02$). Two families, each with a child affected by tics and OCD, demonstrated IgA levels below laboratory reference values [18]. IgA is the second most prevalent antibody in the body after IgG, and appears to act as a silent housekeeper of immune responses. It is a weak activator of complement and down-regulates IgG-mediated phagocytosis the inhibitory effects of which are regulated by binding of its Fc portions to receptors on neutrophils, monocytes, macrophages, and dendritic cells [19]. The implications of these findings for the present study may lie in the interaction of IgA and IgG dysimmunity due to selective deficiency of one or the other Ig in children with PANDAS. Treatment with IVIg has the potential to restore each Ig constituent to normal.

No other study has reported on baseline serum Ig levels in PANDAS or other childhood disorders characterized by tics and OCD in those receiving IVIg therapy [20] although one study found

that IVIg alleviated symptom severity when infection triggered the onset of symptoms.

This study had several limitations by virtue of the available data collected on each case at baseline. First, it was not possible to determine whether IVIg therapy restored circulating Ig levels to normal because data on individual IgA and IgG and subclass levels at the time of follow-up were not available. Second, we hypothesized that frequent GABHS infections might have contributed to the persistence or refractoriness of PANDAS symptoms, but the charts did not contain data on the frequency of GABHS infections before and after IVIg therapy. Third, the follow-up score in the present study rested solely on the determination of a single physician. Finally, as an observational study it provides insight into the real world use and practice of IVIg in the treatment of children with PANDAS, but the results should not be viewed as confirming the safety or effectiveness of IVIg in PANDAS.

Future studies in this area should take into account the baseline

immunologic status of individuals with PANDAS. Studies in larger cohorts are needed to test the hypothesis that IVIg therapy may be effective and safe for subgroups of children with selective IgG and IgG subclass deficiencies. Safety is a concern because children receiving IVIg in the setting of low baseline levels of IgA may be at some theoretical risk of anaphylaxis, but none of the children in our cohort developed anaphylaxis. In addition, further research is needed on the causes and treatment of PANDAS in children without immune deficiencies.

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*Corresponding author: David S. Younger, 333 East 34th Street, 1J, New York NY 10016, USA; E-mail: david.younger@nyumc.org.

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