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Review

Advancing Our Understanding of IVIg in Pediatric Acute-Onset Neuropsychiatric Syndrome

Maria Giovanna Danieli [1,*], Elena Buti [1], Eleonora Longhi [2], Martina Sordoni [1], Martina Bartolucci [1], Sabrina Costanzo [1] and Yehuda Shoenfeld [3,4]

[1] Postgraduate School of Allergy and Clinical Immunology, Dipartimento di Scienze Cliniche e Molecolari, Università Politecnica delle Marche, via Tronto 10/A, 60126 Ancona, Italy
[2] Postgraduate School in Clinical Pathology and Clinical Biochemistry, Università Politecnica delle Marche, via Tronto 10/A, 60126 Ancona, Italy
[3] Dina Recanati School of Medicine, Reichman University, Herzelia 46101, Israel
[4] Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Ramat Gan 52621, Israel
* Correspondence: m.g.danieli@univpm.it; Tel.: +39-(0)-71-220-6105

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Abstract: Intravenous immunoglobulin (IVIg) is a pooled product containing polyclonal IgG collected from the plasma of thousands of healthy donors. Originally developed as a replacement therapy for patients with humoral immunodeficiencies, IVIg has since been widely adopted in the treatment of several autoimmune and inflammatory conditions, owing to its extensive immunomodulatory and anti-inflammatory effects. IVIg exerts a wide range of actions by influencing multiple components of both the innate and adaptive immune systems. These include modulation of Fcγ receptor expression and function, inhibition of complement activation, neutralization of autoantibodies, regulation of cytokine networks, control of pro-inflammatory monocytes, and regulation of multiple immune cells, also through epigenetic modulation. Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) represents one of the most complex conditions in pediatric neuropsychiatry, involving the basal ganglia and characterized by a broad range of abrupt-onset neuropsychiatric symptoms, irrespective of the underlying infectious trigger. Recent clinical and translational studies indicate that IVIg can attenuate neuropsychiatric symptoms and restore immune balance in children with PANS. Randomized trials have produced variable results. Converging clinical and mechanistic evidence supports the potential therapeutic value of IVIg in selected patients with moderate-to-severe or relapsing disease. In this overview, we examine current data on IVIg use in PANS, emphasizing its immunological rationale, emerging clinical benefits, and the need for biomarker-guided studies to better identify responders and optimize treatment outcomes.

Keywords: immune-mediated diseases; intravenous immunoglobulin; monocytes; Pediatric Acute-Onset Neuropsychiatric Syndrome

1. Introduction

Intravenous immunoglobulin (IVIg) is a pooled preparation of polyclonal IgG derived from the plasma of thousands of healthy donors, historically used as replacement therapy for patients with primary or secondary humoral immunodeficiencies [1,2]. Over time, its application has extended to a wide range of autoimmune and inflammatory disorders due to its broad immunomodulatory and anti-inflammatory properties. IVIg exerts pleiotropic effects by targeting various components of both the innate and adaptive immune systems, including modulation of Fcγ receptor expression and function, inhibition of complement activation, neutralization of

autoantibodies, regulation of cytokine networks, and control of pro-inflammatory monocytes [1–3]. These multifaceted mechanisms provide therapeutic benefits in rare and severe immune-mediated conditions that often lack effective treatment. Here, we present an overview of the use of IVIg in Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS), with particular emphasis on its role in regulating dysregulating immune-mediated mechanisms.

2. Pediatric Acute-Onset Neuropsychiatric Syndrome

Pediatric Autoimmune Neuropsychiatric Disorder associated with Streptococcal infections (PANDAS) is an acronym coined in 1998 to describe a group of children with acute-onset neuropsychiatric disorders such as obsessive-compulsive disorder (OCD) and anxiety, related to group A streptococcal infection. [4,5] Over time, broader diagnostic criteria led to the development of PANS (Pediatric Acute-Onset Neuropsychiatric Syndrome), which encompasses a wider spectrum of abrupt-onset neuropsychiatric symptoms, regardless of the infectious trigger [4]. According to the International PANS Registry, patients often present with complex, multisystem involvement and significant functional impairment [4]. The condition is characterized by the sudden onset of obsessive-compulsive symptoms and/or eating restrictions, often accompanied by a range of debilitating neuropsychiatric manifestations. According to established diagnostic criteria, onset must be abrupt and dramatic, typically involving either obsessive-compulsive disorder or food refusal. This is associated with at least two additional neuropsychiatric symptoms, which may include anxiety, depression, emotional lability, irritability, behavioural regression, cognitive decline, sleep disturbances, urinary symptoms, and sensory or motor abnormalities, including complex or simple tics [4,5]. PANS represents one of the most enigmatic and challenging conditions in pediatric neuropsychiatry and is believed to result from a post-infectious inflammatory disorder affecting the basal ganglia. The underlying pathophysiology involves activation of microglial cells, production of pro-inflammatory cytokines, and the presence of autoantibodies directed against neuronal tissue. While group A streptococcal infections have been implicated as potential triggers, a clear temporal association is not always observed. Other infectious agents, such as *Mycoplasma pneumoniae*, Epstein-Barr virus, and more recently SARS-CoV-2, have also been associated with the abrupt onset of similar neuropsychiatric symptoms, possibly via immune-mediated neuroinflammation [4,5].

Previous findings support an immune-mediated and pro-inflammatory model for PANS, which shares clinical overlap with conditions such as PANDAS and Sydenham's chorea, yet remains diagnostically and therapeutically elusive [3]. Recent evidence provides further insight into treatment with IVIg that can reduce both neuropsychiatric symptom severity and the number of circulating pro-inflammatory monocytes, supporting the rationale for immunomodulation in selected patients with severe or persistent PANS [3].

3. IVIg Mechanisms in PANS

Recent data [3,5] provides consistent evidence linking PANS to a pro-inflammatory immune profile. PANS is believed to operate through several key mechanisms as a post-infectious, inflammatory, and autoimmune disorder. Like other autoimmune encephalitis, these processes result in inflammation and microstructural alterations of the basal ganglia, confirmed by neuroimaging studies [6–8]. IVIg modulates this response by neutralizing pathogenic autoantibodies, suppressing cytokine release, and restoring regulatory T-cell function, thereby reducing neuroinflammation and improving neuropsychiatric symptoms. Consequently, early IVIg administration can halt disease progression, normalize basal-ganglia connectivity, and facilitate functional recovery, highlighting its role as a therapeutic option for PANS. Several mechanisms are involved in the immunomodulatory and anti-inflammatory actions of IVIg on both the innate and adaptive immune systems. These actions include Fc-γ receptor blockade, complement inhibition, and modulation of dendritic cell maturation, collectively dampening the inflammatory cascade and promoting immune tolerance (Table 1) [1,2]. However, the precise role of IVIg in PANS has yet to be fully elucidated.

Experimental and clinical evidence suggests that the therapeutic benefits of IVIg therapy derive from the modulation of both soluble mediators and cells of the immune system, as documented in the context of autoimmune and post-infectious conditions [9–12]. Thus, IVIg may restore homeostasis by down-regulating pro-inflammatory cytokines, enhancing regulatory pathways, and facilitating synaptic recovery, which translates into clinical improvement in PANS patients.

Table 1. Main proposed mechanisms of IVIg in PANS.

Modulation of peripheral monocytes activation	Promotes a shift towards a M2-like (regulatory, anti-inflammatory) phenotype, decreasing inflammation
Downregulation of B lymphocytes activity and autoantibodies production	Suppress B lymphocytes production and autoantibodies targeting neuronal tissues
Regulation of autoreactive T cells	The inhibition of activation and proliferation of autoreactive T cells helps to restore immune tolerance
Stabilization of the Blood-Brain barrier	Reduces the immune-mediated damage to the Blood-Brain barrier, thus limiting the entry of autoantibodies and autoreactive cells into the CNS
Modulation of the microglia activation within the CNS	Indirect action on microglia by controlling activated monocytes and proinflammatory cytokines
Inhibition of Fc-gamma Receptor on immune cells	Indirect neutralization of inflammatory cytokines and inflammatory cascades

Abbreviations: CNS, central nervous system; Fc-gamma, fragment, crystallizable portion of IgG antibodies.

Deriving from the pooled IgG of thousands of healthy donors, IVIg possesses a diverse repertoire of antibodies and immunomodulatory molecules acting on various components of the immune system [1,13–15]. Among its functions, one of the most important is the modulation of the complement system: IVIg interferes with complement activation, a cascade of serum proteins that plays a key role in innate and adaptive immune responses [9,15]. In PANS, as in other autoimmune diseases, uncontrolled complement activation can contribute to tissue damage and inflammation. IVIg disrupts this cascade through several mechanisms: inhibition of C1q binding to antigen-antibody complexes, preventing the initiation of the classical pathway, enhancement of C3b and C4b degradation, key components of the complement cascade, recruitment of complement regulators, which further attenuate complement activation, and blockage of the deposition of activated complement fragments [9,12,15].

Moreover, IVIg is involved in the inhibition of Fc receptor-mediated activation, modulating the activation of innate immune cells, such as monocytes and macrophages, through Fc gamma receptors (FcγR). These receptors bind the Fc region of antibodies, triggering intracellular signals that lead to cell activation and the release of inflammatory mediators. IVIg inhibits this process competing with pathogenic immune complexes for binding to FcγR receptors on innate immune cells, preventing cell activation and increasing the expression of inhibitory FcγR receptors, such as FcγRIIB, on innate immune cells [1,15]. This inhibitory receptor counteracts activation signals, suppressing inflammatory responses [10–12,16]. Furthermore, IVIg can induce inhibitory signals, by binding to FcγRIIB, thereby activating intracellular signals that inhibit cell activation and the release of pro-inflammatory cytokines [10,11].

Another important role in immunomodulation by IVIg is the regulation of both T and B cells. IVIg can suppress T cell activation, proliferation, and effector function. This is achieved through various mechanisms, including interference with T cell interaction with antigen-presenting cells (APCs), modulation of cytokine production, and induction of regulatory T cells (Tregs) [17]. On the other hand, IVIg can modulate B cells by increasing the inhibitory receptor FcγRIIB on B cell surfaces [10,16,18]. It has been demonstrated that a reduction in elevated serum levels of B cell activating factor (BAFF) via IVIg treatment, which may lead to a lower activation status of self-reactive B cells, occurs in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) [10–12,18].

A characteristic feature of IVIg is that it contains anti-idiotypic antibodies that can neutralize pathogenic autoantibodies involved in several autoimmune diseases [15]. In PANS, these autoantibodies may target the basal ganglia, contributing to neuropsychiatric symptoms. By neutralizing these autoantibodies, IVIg could reduce tissue damage and inflammation [11,12].

Furthermore, IVIg can influence the production and activity of various cytokines, signaling molecules that play a crucial role in regulating immune responses, as it can suppress the production of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, and promote the production of anti-inflammatory cytokines, such as IL-10 and TGF-β [19]. By modulating the cytokine environment, IVIg can attenuate inflammation and promote immune tolerance [19]. In pediatric patients with OCD and/or movement disorder symptoms, the literature suggests a pro-inflammatory cytokine profile [5]. Studies on these patients have shown significant alterations in the levels of TNF-α, IL-1β, and IL-17 compared to control groups [19]. TNF-α was elevated in patients with OCD, especially in those without PANDAS, and in patients with Tourette's syndrome [19]. IL-1β was also increased in patients with OCD and tics, IL-17A was increased in patients with OCD and Tourette's syndrome. It has been suggested that future studies should include the cytokine IL-23 to clarify its role [19].

Additionally, post-IVIg treatment showed downregulation of pathological epigenetic pathways in a large set of immune cells [20]. The study showed involvement of epigenetic, ribosomal, and immune dysregulation in the

pathogenesis of PANS, affecting through an immune cell-type-specific imbalance. Targeted IVIg regimens aim to correct this imbalance, restoring normal epigenetic signatures and immune homeostasis, which translates into durable symptom relief and functional recovery. The epigenetic machinery, particularly histone methyltransferases, chromatin-remodelling complexes, and the related transcriptional networks, appears to be perturbed in PANS affected patients [20]. Such mechanisms seem to provide a link between the altered immune signaling and the ribosomal involvement. IVIg appears to normalize dysregulated ribosomal protein expression, reducing aberrant protein synthesis that fuels neuroinflammation and supporting synaptic stability in PANS patients [20]. The altered ribosome landscape leads to excessive pro-inflammatory protein translation, which IVIg corrects by stabilizing ribosomal biogenesis, thereby curbing neuroinflammation and promoting synaptic recovery. This epigenetic reprogramming of PANS also seems to correlate with reduced cytokine expression and restored T-cell homeostasis, providing a sustained clinical remission in PANS. Thus, IVIg may restore immune and epigenetic homeostasis, normalize ribosomal function, and dampen neuroinflammation. Crucially, the epigenetic pathways are significantly down-regulated in neutrophils and NK cells, indicating that IVIg may reset epigenetic "memory" that drives the dysregulated transcription-translation program [20]. After treatment with IVIg, previously suppressed immune pathways become up-regulated across most leukocyte subsets, and the abnormal ribosomal enrichment in neutrophils and CD8 T cells is suppressed while NK-cell ribosomal activity normalizes. These immunological shifts correlate with rapid behavioural improvement, offering a plausible therapeutic pathway for PANS symptoms.

Immunoglobulin also appears to have remyelinating potential, leading to limited secondary cellular infiltration and thus protection from further injury. Removal of myelin-associated inhibitors present in central and peripheral nervous system lesions may play a role in this process. IVIg leads to increased uptake of myelin debris by macrophages in vitro, which is thought to support and accelerate subsequent remyelination and improve neurological outcomes [12]. Studies have shown that antibodies that recognize myelin basic protein can promote central nervous system remyelination, further linking immunoglobulin-mediated myelin handling to repair processes [21]. By promoting oligodendrocyte survival and enhancing myelin sheath repair, IVIg may preserve neural connectivity, reduce relapse risk, and support long-term functional recovery in children with PANS. Future research should quantify remyelination biomarkers and assess long-term neurocognitive outcomes to validate IVIg's role [21].

Another noteworthy aspect is the suggested association between PANS and immunodeficiency. In a report with a median follow-up of 3.3 years in children with PANS, deficiencies in serum IgG subclasses were observed in 11/27 (41%) patients, while low serum IgA levels were found in 6/27 (22%). Additionally, six children (22%) presented with complement abnormalities [22]. In a 2023 retrospective study, Eremija et al. [23] reported that 5/12 children with PANS had hypogammaglobulinemia requiring IVIg replacement therapy. One more patient exhibited isolated low serum IgA levels. A humoral deficiency may account for the increased susceptibility to, or the recurrence of, infections in these children, as well as the observed benefit of IVIg therapy in some cases [24]. However, the current evidence is too scarce to draw definite conclusions.

4. IVIg Treatment in PANS

The therapeutic role of IVIg in PANS and PANDAS remains an area of significant scientific interest and clinical controversy. Early controlled studies demonstrated robust improvement in obsessive–compulsive symptoms with both IVIg and therapeutic plasma exchange, suggesting that immunomodulation may modify the neuropsychiatric manifestations of these disorders [25]. Multiple case reports and series further strengthened the rationale for immune-targeted therapy. However, more recent randomized trials have shown inconsistent results, with symptom improvement often emerging only after open-label IVIg administration [25]. These discrepancies highlight methodological challenges, including expectation effects, spontaneous symptom fluctuation, and the relapsing–remitting nature of the disease, which can obscure true treatment efficacy. Notably, biomarker analyses indicate that specific immunologic signatures—such as elevated anti-neuronal antibodies and CaM-KII activation—and neuroimaging evidence of basal ganglia inflammation may predict response to IVIg [25]. While current data do not support widespread routine use, early trial success and biologically grounded response patterns justify further rigorously designed and stratified clinical studies [25].

Expanding on these foundational observations, recent single-cell RNA sequencing studies provide additional mechanistic insight into how IVIg may exert broad immunomodulatory and even epigenetic effects [20]. At baseline, children with PANS displayed immune dysregulation characterized by altered NK cell signaling and downregulation of ribosomal and immune pathways. Following IVIg administration, these transcriptomic abnormalities were largely reversed, suggesting restoration of immune homeostasis and introducing the possibility

that IVIg acts in part through chromatin remodeling. Nevertheless, despite these biological changes, clinical benefits are often transient—lasting only several weeks—and prior trials have not consistently demonstrated superiority over placebo. These findings further underscore the need for larger blinded studies and for identifying predictors of treatment response to ensure appropriate patient selection [20].

In parallel with biomedical advances, parental perspectives have emerged as a critical factor influencing treatment decisions and outcomes [26]. Recent findings show that families generally view inflammation- and infection-targeted interventions—such as antibiotics, non-steroidal anti-inflammatory drugs, and IVIg—as the most appropriate options, while psychiatric and more invasive neuromodulatory treatments are perceived as less acceptable due to concerns about pediatric use and limited supporting evidence. This highlights the importance of individualized, multimodal strategies incorporating immunomodulation, infection control, and behavioral therapies—such as exposure and response prevention—to address residual obsessive–compulsive symptoms. Strengthening communication and shared decision-making may ultimately improve adherence and long-term prognosis.

Supporting these real-world clinical perspectives, retrospective and prospective studies, including those by Eremija et al. [23], demonstrate measurable neuropsychiatric improvement following repeated IVIg cycles, even when dosing protocols vary. These results align with earlier work [25] and suggest that symptom reductions may reflect restoration of immune balance in biologically vulnerable patients. To improve comparability across future studies, the adoption of standardized neuropsychological assessment tools is recommended, as they can more accurately quantify treatment response and minimize bias inherent in subjective rating scales. Positive responses to IVIg and other immunomodulatory interventions further support immune dysfunction as a core pathophysiologic mechanism in PANS [23].

Mechanistic research continues to clarify which patients are most likely to benefit [27]. Converging evidence indicates that IVIg may be particularly effective in antibody-mediated PANDAS. Autoantibodies from affected individuals bind striatal cholinergic interneurons and disrupt their function, linking immune dysregulation to basal ganglia–driven neuropsychiatric symptoms. IVIg reduces both antibody binding and associated physiological impairment, with parallel improvements in obsessive–compulsive and tic symptoms. Nevertheless, clinical heterogeneity remains substantial—likely reflecting the variable presence of immunopathologic features such as Cholinergic Interneuron (CIN)-specific autoantibodies or biomarkers of neuroinflammation. Thus, future trials incorporating biomarker-driven stratification will be essential to define responders and establish IVIg as a targeted therapy within the broader PANS/PANDAS spectrum [27].

Further illustrating the interplay between infection and immunity, a compelling clinical case showed that IVIg contributed to full recovery in a patient with PANDAS and persistent Lyme disease [28]. The patient experienced multiple streptococcal infections and tested positive for Borrelia burgdorferi across independent laboratories. Sudden and dramatic onset of cognitive decline, anxiety, panic, obsessive–compulsive symptoms, and aggression suggested basal ganglia encephalitis. A 31-month treatment course combining antimicrobial therapy with three cycles of IVIg resulted in complete remission, accompanied by normalization of elevated anti-neuronal antibodies on the Cunningham Panel™. This case illustrates that addressing both infectious triggers and immune dysregulation can lead to sustained recovery, supporting an autoimmune basis for infection-triggered neuropsychiatric disorders such as PANS/PANDAS [28].

Encouragingly, more structured clinical trials have also demonstrated benefit. For example, Melamed et al. [3] assessed IVIg (Octagam 5%) in children aged 4–16 years with moderate to severe PANS using a pediatric-adapted dose (1 g/kg every 21 days for six infusions). Symptom reductions exceeded 50% on the Children's Yale–Brown Obsessive Compulsive Scale (CY-BOCS) and Clinical Global Impression–Severity (CGI)-scale ($p < 0.0001$), and improvements persisted up to 46 weeks after treatment. Gains in fine motor skills, emotional expression, and parent-rated outcomes further supported clinically meaningful benefit. Although these findings require confirmation in randomized placebo-controlled studies, they show that sequential IVIg infusions can produce sustained neuropsychiatric improvement [3].

In contrast, a systematic review by Johnson et al. [29] noted that the overall evidence base remains weak due to small sample sizes and methodological limitations. One randomized controlled trial and one open-label study [25,30] reported variable findings—improved global functioning in some patients, but no statistically significant changes in obsessive-compulsive symptoms. Unblinding due to recognizable side effects further complicated interpretation. Still, the review by Johnson et al. [29] acknowledged that IVIg is generally safe and may benefit select patient groups, reinforcing the need for rigorous placebo-controlled trials using standardized diagnostic criteria. Adding to the growing clinical evidence, a prospective open-label trial of monthly IVIg (2 g/kg for three months) in ten children with PANS reported a 42% reduction in total symptom burden, with nine of ten patients meeting response criteria and considerable improvements in school participation. Adverse events were mild and

transient. These results support an immune-mediated pathophysiology and suggest a potential role for repeated IVIg courses in appropriate cases [30].

Taken together, these findings support IVIg as a central therapeutic option for moderate-to-severe or refractory PANS/PANDAS, consistent with the presumed autoimmune basis shared with related conditions such as Sydenham's chorea, Guillain–Barré syndrome, and autoimmune encephalitis. A double-blind, placebo-controlled trial in PANDAS demonstrated a 45% reduction in obsessive-compulsive symptoms with IVIg, and positron emission tomographic (PET) imaging studies have shown decreased microglial activation following therapy [31]. Current recommendations suggest an induction dose of 1.5–2 g/kg, with additional monthly courses for acute, moderate-to-severe, or relapsing disease. Early initiation appears to be associated with better outcomes and fewer relapses. While most adverse effects are mild and manageable—such as post-infusion headaches—serious reactions remain rare [31].

Finally, emerging case reports continue to expand the spectrum of infectious triggers leading to PANS/PANDAS-like presentations. An illustrative example involves adolescent twin sisters who developed severe neuropsychiatric symptoms following SARS-CoV-2 exposure. Despite negative PCR results, positive IgG serology supported prior infection. Neurological and psychiatric manifestations were broad and debilitating, yet IVIg introduced after one month led to marked improvement within a week, including restoration of nutritional intake and resolution of disabling symptoms. This report underscores that SARS-CoV-2 may act as a relevant trigger for PANS, even without respiratory involvement, further emphasizing the need to integrate immunological evaluation in acute-onset pediatric neuropsychiatric cases. [32]

5. Conclusions

A full understanding of the specific mechanisms through which IVIg exerts its therapeutic effects in PANS and other autoimmune and post-infectious conditions requires further research. Identifying molecular markers that can predict the response to IVIg treatment will be valuable for personalizing therapy and optimizing patient outcomes. Given the heterogeneity of the various autoimmune disease conditions that respond to IVIg, it is likely that different disease-specific pathways mediate the clinical efficacy of this agent for a given disease. Therefore, it is difficult to identify a general mechanism for the anti-inflammatory or immunomodulatory efficacy of IVIg. Taken together, IVIg's ability to modulate monocyte function, inhibit inflammatory cytokine production, restore immune tolerance, and prevent excessive immune activation underlies its efficacy across multiple autoimmune and inflammatory conditions. IVIg represents a valuable therapeutic resource, but increasing demand and high costs require the development of alternative strategies, such as the production of recombinant proteins with immunomodulatory activities like those of native IgG.

Author Contributions

M.G.D. and Y.S. were responsible for the review design. E.B., E.L., M.S., M.B. and S.C. conducted the primary review of the studies and contributed significantly to the writing of the first draft. All Authors contributed to the analyses of the references and revised the manuscript critically. All authors have read and agreed to the published version of the manuscript.

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Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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