

1. To begin, could you tell us a little about yourself, your medical training and current work, and how you became involved in treating children with PANS/PANDAS and other neuroimmune conditions?

Answer:

I am a neurologist and medical geneticist, founder of Vivere Clinic, and President of the Neuroimmunology Association of Ukraine. My main professional areas are neuroimmunology, genetics, and the diagnosis and treatment of complex neurological and neurodevelopmental disorders in children.

I graduated from Dnipropetrovsk State Medical Academy and initially trained in internal medicine. I subsequently completed additional specializations in neurology, healthcare organization and management, and medical genetics.

At the beginning of my professional career, I primarily worked with children with organic disorders of the central nervous system, psychomotor developmental delay, and other complex neurological conditions.

During that period, I began noticing a trend that significantly influenced my subsequent professional path. I was seeing a gradual increase in the number of children diagnosed with autism spectrum disorder. This led me to a fundamental question: why was this happening?

I wanted to understand the biological mechanisms underlying these disorders—why some children show atypical development from the beginning, while others initially develop according to age expectations but later lose previously acquired skills.

I became particularly interested in the role of the immune system in brain development and function. I began studying in greater depth the relationships between infectious diseases, autoimmune responses, neuroinflammation, genetic susceptibility, and neurodevelopmental disorders.

More than ten years ago, neuroimmunology therefore became one of the principal areas of my clinical and scientific work.

Over time, children with PANS/PANDAS became an important part of my practice. I observed cases in which infections were followed by sudden and sometimes dramatic behavioral and neurological changes: tics, obsessive-compulsive symptoms, severe anxiety, aggression, sleep disturbances, enuresis, food restriction, or regression of previously acquired skills.

These cases were particularly challenging in children who already had a diagnosis of autism. New symptoms were often attributed to the underlying neurodevelopmental disorder, even though their sudden onset and clinical course warranted further investigation.

This strengthened my conviction that understanding complex neurological and neuropsychiatric conditions requires an integrated approach combining neurology, immunology, genetics, infectious diseases, and metabolic medicine.

Today, a significant proportion of my clinical practice involves children with autism, developmental regression, epilepsy, PANS/PANDAS, and other complex conditions. We work with patients from Ukraine and many other countries, and in every case we try not to stop at a diagnostic label but to investigate the possible mechanisms underlying the child's condition as deeply as possible.

My professional philosophy is that **a diagnosis is not the end of the diagnostic process; it is the beginning of understanding the mechanisms of disease.** This principle has guided my work for more than a decade.

2. How long have you been working with these children, approximately how many PANS/PANDAS patients have you evaluated, and from which countries do your patients come? Have you also worked with a significant number of children from Romania?

Answer:

I have been involved in the diagnosis and treatment of children with PANS/PANDAS for approximately ten years. During this period, our clinic has accumulated substantial clinical experience.

Overall, approximately **11,000 children** with various neurological, neurodevelopmental, genetic, and neuroimmune disorders have been evaluated in our practice. Of these, approximately **2,000 children have had PANS/PANDAS.**

Our clinical work is now international. Families from more than **40 countries** have consulted us. We work particularly actively with patients from Ukraine and other European countries, including Romania.

Recently, the number of Romanian children referred to us has increased considerably. We see both classical PANS/PANDAS presentations with acute onset and more complex situations in which neuroimmune abnormalities coexist with autism, developmental delay, epilepsy, or other neurological disorders.

One of the most interesting observations from years of international practice has been the apparent variation in potential disease triggers among children from different countries and populations.

We observe that the spectrum of infectious agents, patterns of immune abnormalities, and clinical manifestations may differ according to the patient's geographic background. This may reflect differences in circulating infectious pathogens, genetic susceptibility, environmental conditions, and other factors.

However, it is important to emphasize that these are currently **clinical observations that require further scientific validation.** Nationality itself does not determine the mechanism of disease.

The large number of patients and international nature of our practice allow us to compare different clinical phenotypes, analyze potential triggers, and continue refining individualized approaches to diagnosis and treatment.

For me, it is essential to remember that PANS/PANDAS is primarily a **clinical diagnosis requiring careful differential diagnosis**. Not every child with autism, tics, or behavioral abnormalities has a neuroimmune disorder.

Our primary objective is to determine whether a pathological immune process is present in a particular child, identify possible triggers, and develop the most appropriately justified personalized treatment strategy.

3. What outcomes have you observed in your clinical practice? How often do you see substantial improvement or remission, and what seems to distinguish children who respond very well from those with more difficult or refractory cases?

Answer:

Outcomes vary considerably.

There are children in whom identification and appropriate treatment of the relevant trigger are followed by substantial improvement, sometimes approaching a complete return to premorbid functioning. However, there are also much more complex cases involving years of illness, recurrent exacerbations, and multiple overlapping pathological mechanisms.

The best responses are more commonly seen when the onset of the disease is clearly defined, a potential trigger can be identified, and treatment is initiated relatively early.

Refractory cases are often more complex not because of a single factor, but because of a combination of genetic susceptibility, immune dysregulation, recurrent infections, persistent neuroinflammation, and an underlying neurodevelopmental disorder.

Therefore, my objective is not simply to assign the label of PANS to a child, but to understand **the mechanisms driving the disease in that particular child**.

4. From a medical perspective, how do you conceptualize PANS/PANDAS? Where do you place it in relation to neuroinflammation, autoimmunity, and autoimmune encephalitis or encephalopathy?

Answer:

I consider PANS/PANDAS primarily a **clinical syndrome rather than a single etiologically homogeneous disease**.

PANDAS is a narrower concept involving an association with streptococcal infection. PANS is a broader syndrome in which potential triggers may include a variety of infectious and non-infectious factors.

In a subset of children, I believe that a pathological immune response involving neuroinflammation and functional disruption of neuronal networks may represent an important mechanism.

At the same time, I do not believe that PANS should automatically be equated with autoimmune encephalitis. They represent a spectrum of clinically and pathophysiologically distinct conditions. There may be overlapping mechanisms in some patients, but the diagnostic criteria for classical autoimmune encephalitis are considerably more stringent.

5. What do you believe is actually happening in the brain of a child with PANS/PANDAS, and why are the basal ganglia considered so important in symptoms such as OCD, tics, motor abnormalities, behavioral changes, and cognitive difficulties?

Answer:

One of the leading hypotheses is that a particular immune trigger initiates a pathological immune response that can subsequently affect neuronal network function.

The **cortico-striato-thalamo-cortical circuits and basal ganglia** are of particular interest. These structures are involved not only in motor control but also in behavior, habit formation, motivation, and obsessive-compulsive symptoms.

Dysfunction within these networks could therefore theoretically explain why the same child may simultaneously develop tics, OCD, abnormal motor phenomena, emotional lability, and cognitive changes.

However, it is important to recognize that we still do not have a single proven mechanism capable of explaining every case of PANS.

6. What relationship do you observe between PANS/PANDAS and autism? How often do you see them occurring in the same child? Do you generally view them as separate conditions that can coexist, or do you also see a subset of children in whom a neuroimmune process may significantly influence their developmental and neuropsychiatric presentation?

Answer:

This is one of the most important issues in my clinical practice because a significant proportion of our patients are children with autism spectrum disorders and complex neurodevelopmental conditions.

First, I want to emphasize that **autism is a clinically and biologically heterogeneous condition**. Similar behavioral phenotypes may result from different genetic syndromes, metabolic diseases, epileptic encephalopathies, and other pathological processes associated with an autistic phenotype.

For this reason, I try not to stop at the diagnosis of ASD, but rather to investigate as deeply as possible the biological mechanisms affecting the development of the individual child.

According to our clinical observations, PANS/PANDAS occurs approximately **four times more frequently in children diagnosed with ASD than in children with typical neurodevelopment**. This is a preliminary observation from our specialized clinical population rather than an established epidemiological figure and therefore requires validation in controlled studies.

Particular attention should be paid to situations in which PANS/PANDAS becomes superimposed on an existing somatic, genetic, metabolic, or neurological disorder associated with an autistic phenotype.

Such a child already has abnormalities of development and central nervous system function. Later, often following an infection, a new group of symptoms may appear: obsessive-compulsive manifestations, tics, severe anxiety, emotional instability, aggression, sleep disturbance, changes in eating behavior, or loss of previously acquired skills.

The clinical picture then becomes considerably more complex. Parents frequently describe it by saying, **“My child already had autism, but after the illness everything suddenly became much worse.”**

Unfortunately, these new symptoms may automatically be attributed to progression of the underlying neurodevelopmental disorder. Consequently, superimposed PANS/PANDAS may remain unrecognized.

I consider it essential to distinguish between two pathological processes: the underlying condition responsible for the autistic phenotype and a potentially superimposed neuroimmune syndrome such as PANS/PANDAS. They can coexist, but they should not automatically be regarded as manifestations of the same disease.

This distinction has major practical implications. When concomitant PANS/PANDAS is correctly identified and appropriately treated, some children may show substantial improvement in behavior, sleep, emotional regulation, attention, and everyday functioning.

However, such improvement does not mean that the underlying disease has been cured or that autism has been eliminated. Rather, we may have successfully treated an additional pathological process that was worsening the child's condition.

Of course, not every deterioration in a child with ASD represents PANS/PANDAS. Established clinical criteria must be met, and developmental regression requires exclusion of other neurological, genetic, metabolic, and systemic causes.

The key point is that **two different disorders may coexist in the same child**: an underlying disease associated with an autistic phenotype and superimposed PANS/PANDAS. If we fail to

distinguish these processes, we risk missing a potentially reversible component of the child's deterioration.

7. In a child who already has an autism diagnosis, what changes or symptoms would prompt you to investigate PANS/PANDAS as a possible comorbidity? Conversely, what helps you distinguish features related to the child's underlying neurodevelopmental profile from a superimposed neuroimmune process?

Answer:

This is a broad subject, but I would focus on the main clinical signs and one central principle.

The most important warning sign is **a change from the child's usual baseline**, particularly when it occurs suddenly or over a relatively short period.

Important red flags include sudden onset of obsessive-compulsive behavior or new rituals, or a marked worsening of pre-existing rituals; new tics, repetitive movements, or unusual motor phenomena; severe anxiety, new fears, emotional instability, irritability, or aggression; abrupt sleep disturbance or new nighttime awakenings; sudden food restriction or refusal to eat; new-onset enuresis or urinary frequency without an obvious urological explanation; and deterioration in attention or cognitive functioning, or loss of previously acquired skills.

It is particularly important to establish whether an infection or another significant event preceded these changes. However, a temporal association with infection alone does not prove PANS/PANDAS.

A crucial principle is that **having autism does not mean that every new neurological or behavioral symptom should be attributed to autism**.

We need to distinguish manifestations of the underlying condition from a newly emerging pathological process. For PANS specifically, the acute onset of OCD or severe restrictive food intake together with other characteristic manifestations is particularly important.

Aggression, sleep disturbance, or regression alone are insufficient to establish the diagnosis.

My main recommendation to parents and physicians is therefore to take any sudden change in a child's condition seriously. Do not automatically attribute it to autism. The cause of deterioration needs to be investigated because it may represent a separate condition, including PANS/PANDAS, requiring its own diagnostic and therapeutic approach.

8. Have you treated children previously diagnosed with autism, ADHD, OCD, or other neuropsychiatric conditions in whom an associated infectious or immune component was subsequently identified and treated, resulting in significant clinical changes? If so, which symptoms or abilities tend to improve, and which characteristics tend to remain?

Answer:

Yes, and this represents one of the most important areas of our clinical practice.

Over the years, we have accumulated substantial experience treating children in whom PANS/PANDAS developed in addition to an underlying neurodevelopmental, genetic, or other disorder.

The treatment outcomes in many cases are very encouraging. **According to our clinical observations, in approximately half of cases we are able to achieve complete resolution of PANS/PANDAS symptoms.** It is important to emphasize that this figure reflects our clinical experience and is not the result of a controlled study. Scientific validation would require standardized definitions of complete remission, standardized follow-up periods, and standardized outcome assessment.

We most commonly observe substantial improvement or complete resolution of obsessive-compulsive symptoms, tics, severe anxiety, aggression, emotional instability, and sleep disturbances. In some children, normal eating behavior returns and attention, communication, learning ability, and everyday functioning also improve.

Particularly striking are cases in which parents report that the child has returned to the state they were in before the onset of the acute neuropsychiatric syndrome.

However, I always explain to families the fundamental distinction between **eliminating PANS/PANDAS symptoms and treating the underlying disease.**

For example, if a child has a genetic or another disorder associated with an autistic phenotype, successful treatment of concomitant PANS/PANDAS may completely resolve the additional neuropsychiatric symptoms. The baseline neurodevelopmental features associated with the underlying condition may nevertheless remain.

It is therefore essential to distinguish between two outcomes: treatment of the underlying disorder and resolution of superimposed PANS/PANDAS.

Even when we cannot eliminate the underlying genetic or neurodevelopmental condition, we should identify and treat additional pathological processes that are worsening the child's clinical state.

When complete remission of PANS/PANDAS is achieved, it can substantially change the quality of life not only for the child but for the entire family.

9. How do you approach very young children, in whom an acute onset may be difficult to document and who cannot yet describe obsessions, intrusive thoughts, or anxiety? Can developmental regression sometimes be an important signal that warrants a broader medical and neuroimmune evaluation?

Answer:

In very young children, applying the classical criteria is considerably more difficult.

A two- or three-year-old child cannot tell us, “I have developed intrusive thoughts.” We therefore assess behavioral equivalents: sudden rituals, fears, food restriction, separation anxiety, sleep disturbances, motor phenomena, and particularly developmental regression.

However, **regression in a young child is not synonymous with PANS**. It is an indication for broad differential diagnosis, including genetic, metabolic, epileptic, structural, infectious, and immune causes.

10. Which investigations do you consider genuinely important in the initial evaluation of a child with suspected PANS/PANDAS?

Answer:

We use a staged diagnostic approach to PANS/PANDAS.

According to our clinical observations, the spectrum of potential infectious triggers may vary depending on the geographic region and population from which the child comes. We therefore consider not only the clinical presentation but also the epidemiological characteristics of the patient's region of residence.

The first stage consists of basic laboratory investigations, assessment of the immune system, and investigation of the most common potential infectious triggers.

Initial investigations usually include a complete blood count, basic biochemical parameters, inflammatory markers such as CRP and ESR, and immunological assessment, including an immunogram evaluating the major lymphocyte populations and immunoglobulin levels.

Particular attention is given to potential infectious triggers. We initially assess a possible association with streptococcal infection and, where clinically and epidemiologically appropriate, *Mycoplasma pneumoniae*, viral infections, and other infectious agents.

The objective is not simply to detect antibodies against a particular pathogen, but to determine whether that infection may be clinically relevant in the individual case.

Where possible, I also recommend considering brain MRI, particularly in children with complex neurological symptoms, developmental regression, or an atypical disease course. MRI can help assess brain structures and exclude alternative organic causes. However, it is not mandatory for every child with a typical PANS/PANDAS presentation, and a normal MRI does not exclude the syndrome.

If abnormalities are found during the initial assessment, or if the clinical picture remains unclear, we proceed to more extensive investigations. These may include advanced immunological studies, EEG, neuronal autoantibody testing, genetic and metabolic investigations, and, in selected cases, cerebrospinal fluid analysis.

PANS/PANDAS remains primarily a **clinical diagnosis**. No immunogram, infectious test, or MRI can independently establish it.

My main principle is to begin with accessible basic investigations, immune-system assessment, and the most likely infectious triggers for the relevant region, and then progressively deepen the diagnostic work-up according to the findings.

This approach helps avoid unnecessary testing and financial burden for families while reducing the risk of missing clinically important abnormalities.

11. What clinical value do you assign to the Cunningham Panel, CaMKII activity, and broader neuronal autoantibody panels, including antibodies against D1/D2 receptors, NMDA receptors, gangliosides, tubulin, or Purkinje cells? Can a child still have a convincing clinical presentation of PANS/PANDAS when these tests are normal?

Answer:

First, I would like to clarify that the test previously known as the **Cunningham Panel is now called the Autoimmune Brain Panel**.

We use this panel in clinical practice, but we do not regard it as a standardized or mandatory investigation for every child with suspected PANS/PANDAS.

We most commonly use it in complex or diagnostically controversial cases, where the clinical picture is ambiguous, an autoimmune component is suspected, and the basic investigations do not provide a sufficiently clear understanding of the potential disease mechanisms.

The principal advantage of the panel is that it may provide additional information about the possible involvement of antibody-mediated mechanisms in the pathological process.

In some cases, the results can help formulate a clinical hypothesis and determine which additional investigations should be performed before deciding on the subsequent treatment strategy.

However, there is an important limitation: the panel is not yet sufficiently validated as a diagnostic tool for PANS/PANDAS, and its ability to predict the efficacy of specific immunotherapies has not been established. We therefore do not initiate immunomodulatory treatment solely on the basis of a positive panel or elevated CaMKII activity.

The same principle applies to broader neuronal autoantibody testing. The significance of these antibodies depends on the specific antigen, laboratory methodology, clinical phenotype, and the presence of other objective evidence of central nervous system disease.

Importantly, **a normal Autoimmune Brain Panel does not exclude PANS/PANDAS**. At present, there is no laboratory biomarker capable of independently confirming or excluding the syndrome with complete accuracy.

I therefore regard the Autoimmune Brain Panel as an adjunctive tool for selected complex cases rather than a universal diagnostic standard. Its findings may complement clinical

assessment and inform discussion of the therapeutic strategy, but they should never replace clinical reasoning or independently determine treatment.

12. What roles do EEG and lumbar puncture play in your evaluation? When do you consider them necessary, and what findings could actually change your therapeutic approach?

Answer:

EEG is particularly important when there are episodes of altered consciousness, language regression, paroxysmal phenomena, nocturnal episodes, or suspicion of an epileptic encephalopathy.

Lumbar puncture is not necessary for every child with PANS. I consider it in severe or atypical presentations, altered consciousness, seizures, prominent movement disorders, or when infectious or autoimmune encephalitis needs to be excluded.

In such circumstances, cerebrospinal fluid analysis may fundamentally change both the diagnosis and treatment strategy.

13. What can brain MRI show in PANS/PANDAS? Can a child with severe symptoms still have a conventional MRI that is interpreted as normal?

Answer:

Brain MRI is an important additional investigation in children with suspected PANS/PANDAS, particularly in complex clinical presentations or when significant neurological symptoms are present.

We pay particular attention to the **basal ganglia**, especially the caudate nucleus, putamen, and globus pallidus.

The basal ganglia are involved not only in motor regulation but also in behavior, emotional responses, and obsessive-compulsive phenomena.

Scientific studies of PANDAS have described changes in basal ganglia volume, including enlargement. This is an interesting structural finding supporting the hypothesis that these brain regions may be involved in the pathological process.

Of particular interest is the possibility that pathologically increased basal ganglia volume may decrease over time, including in association with clinical improvement following treatment. Such changes have been described in individual observations, although there is currently insufficient evidence to regard this as a consistent or specific treatment response.

In clinical practice, such findings can provide useful additional information as part of a comprehensive assessment. However, basal ganglia enlargement is **not an established diagnostic criterion for PANS/PANDAS**, nor does it independently prove neuroinflammation.

It is also important to understand that even a child with severe PANS/PANDAS can have a completely normal conventional structural MRI. The absence of visible structural abnormalities does not exclude dysfunction of neuronal networks or possible immune-mediated mechanisms.

MRI is also important for excluding alternative causes of neurological symptoms, including structural abnormalities, demyelinating disease, tumors, and sequelae of encephalitis.

The central point is therefore that basal ganglia abnormalities may represent an important additional finding in PANS/PANDAS, and their longitudinal evolution may be clinically informative; however, the diagnosis remains primarily clinical rather than MRI-based.

14. Do you use volumetric analysis of the basal ganglia? If so, what software or methodology do you use, how do you interpret abnormal volumes, and have you observed changes in these structures following treatment?

Answer:

Yes. In selected cases, quantitative assessment of brain structures may be useful as an additional clinical and research tool.

The caudate nucleus, putamen, globus pallidus, and other basal ganglia structures are of particular interest.

However, I do not use an increase or decrease in their volume as an independent diagnostic criterion for PANS/PANDAS. Such findings need to be interpreted in relation to age, total brain volume, the normative database of the particular software, the clinical presentation, and longitudinal changes.

An especially interesting direction for future research is **longitudinal MRI**, comparing quantitative measurements before and after treatment.

15. How do you determine whether an infectious finding represents a clinically relevant trigger? What weight do you give to IgG/IgM serology compared with PCR, culture, or other direct detection methods when trying to distinguish previous exposure from active or persistent infection?

Answer:

A positive laboratory test does not necessarily mean that the detected infection caused the neuropsychiatric symptoms.

IgG most commonly indicates previous exposure and does not, by itself, establish active infection. IgM must also be interpreted cautiously because of possible persistence and false-positive results.

Where appropriate, direct methods such as PCR, culture, or antigen detection provide different information. However, even a positive PCR must be interpreted within the clinical context.

The most important factor is the **totality of the evidence**: clinical presentation, temporal relationship, laboratory findings, and biological plausibility.

16. Beyond Group A Streptococcus, which infections do you encounter most frequently in your patients? What role do you believe Mycoplasma, viruses, Borrelia, Bartonella, or other infectious agents may play?

Answer:

After almost ten years of working with PANS/PANDAS and evaluating children from more than 40 countries, we have noticed an interesting feature: **the spectrum of potential infectious triggers may vary according to geographic region and patient population.**

In our clinical experience, there appear to be differences among children from Europe, Asia, and North America. These may reflect differences in infection prevalence, climate and environmental factors, living conditions, and genetic characteristics of the immune response. However, these observations require confirmation in systematic comparative studies.

The best-known infectious agent associated with PANDAS remains *Streptococcus pyogenes*, group A beta-hemolytic streptococcus.

However, we consider a much broader spectrum of potential infectious factors.

These include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Borrelia* species associated with Lyme disease, *Bartonella*, and various viral infections.

I would also specifically mention **SARS-CoV-2 (COVID-19)**. Since the pandemic, greater attention has been paid to cases in which neuropsychiatric symptoms appear or worsen following COVID-19. SARS-CoV-2 infection can be associated with immunological and neurological complications, although its direct causal role in PANS remains under investigation.

Another group that should not be ignored when clinically and epidemiologically appropriate is **parasitic infection**. Depending on the geographic region, protozoal infections and helminthiases may need to be considered because they can affect immune responses and the child's overall health. At present, however, there is insufficient evidence to regard parasitic infections as typical direct triggers of PANS/PANDAS.

We therefore do not apply an identical infectious-disease diagnostic algorithm to every patient. We consider country of residence, epidemiological history, previous illnesses, the pattern of symptom onset, and previous test results.

It is essential to distinguish active infection from evidence of past exposure. Positive IgG, and sometimes even IgM, does not necessarily indicate active infection, and detection of an infectious agent does not prove that it caused the neuropsychiatric symptoms.

The key message is that **the spectrum of potential infectious triggers in PANS extends beyond streptococcus, and geographic and population differences should be considered during the diagnostic process.** Our task is not simply to find an infection, but to establish its actual clinical significance for the individual child.

17. When a child appears to have both an infectious component and immune dysfunction/neuroinflammation, how do you determine the order of treatment? Should the infection be addressed first, or can antimicrobial and immunomodulatory treatment proceed simultaneously?

Answer:

Whenever possible, the first objective is to **identify and eliminate the infectious or other trigger** that may have initiated the pathological immune response.

In practice, however, this cannot always be accomplished quickly. Identifying a potential trigger may require time, additional laboratory investigations, and specialist assessment. In some cases, the original infection has already resolved while the neuropsychiatric symptoms persist.

At the same time, the child may have severe manifestations such as intense anxiety, obsessive-compulsive symptoms, tics, aggression, sleep disturbance, or substantial deterioration in everyday functioning.

In these circumstances, we cannot always wait until the trigger has been definitively identified. Anti-inflammatory treatment may therefore be initiated while the diagnostic investigation continues. Treatment selection depends on disease severity, clinical indications, and investigation results. Before systemic immunosuppression, the risk of active infection must be carefully assessed.

When a clinically significant infection is confirmed, appropriate etiological treatment is used. Depending on the pathogen, this may include **antibacterial, antiviral, or antiparasitic therapy**. Such treatment should have a specific indication rather than being prescribed empirically simply because the child has PANS/PANDAS.

In selected patients, treatment of the infection and anti-inflammatory therapy may proceed simultaneously under appropriate medical supervision.

We must also recognize that symptoms may persist after the initial trigger has been eliminated. Treatment therefore needs to address not only a potential infectious factor but also the child's clinical manifestations and functional status.

The main principle is simple: **if the trigger is identified, we try to eliminate it. If it cannot be identified quickly and the child's condition requires treatment, we do not unnecessarily delay justified treatment of the inflammatory component while continuing the diagnostic investigation.**

18. At what point do you consider antibiotics and anti-inflammatory treatment insufficient and begin considering IVIG? What are your main criteria for selecting patients for IVIG?

Answer:

I do not consider IVIG to be first-line therapy for every child with suspected PANS.

I consider IVIG when the clinical presentation is severe and significantly impairs the child's functioning, when there is evidence supporting an immune-mediated mechanism, and when simpler approaches have been insufficient or the clinical situation does not permit prolonged delay.

Particularly important considerations include disease severity, clinical trajectory, objective evidence of immune dysregulation, and exclusion of alternative diagnoses.

19. How do you use IVIG in your practice: what dosing strategy do you generally use, when do you repeat treatment, how long do you wait before assessing the response, and how do you distinguish a temporary post-IVIG worsening from treatment failure or a true disease flare?

Answer:

When IVIG is used for immunomodulation, the regimen should be determined according to the clinical situation, body weight, comorbidities, and treatment tolerability.

It is very important **not to assess the response too early**. During the first days following infusion, some children may experience headache, fatigue, irritability, or temporary worsening of symptoms. This does not necessarily indicate treatment failure.

Clinical response should be assessed comprehensively, including overall functioning, OCD symptoms, tics, sleep, behavior, learning, language, and other symptoms documented before treatment.

The decision to repeat IVIG should not be automatic. It should depend on the objective clinical response and subsequent course of the disease.

20. How important is the duration of illness? Can a child who has remained undiagnosed or insufficiently treated for several years still achieve substantial recovery with appropriate antimicrobial and/or immunomodulatory treatment?

Answer:

Early recognition is very important, but a long disease history does not mean that treatment is no longer worthwhile.

I have seen children with longstanding disease who experienced substantial improvement following appropriate diagnosis and treatment.

At the same time, the longer the disease has been present, the more difficult it becomes to distinguish an active pathological process from secondary behavioral changes, psychiatric comorbidity, and the consequences of prolonged functional maladaptation.

I therefore do not promise “complete recovery,” but neither do I consider a history of several years to be a reason to stop searching for potentially reversible factors.

21. How do you define refractory PANS/PANDAS, and at what point do you consider therapeutic plasma exchange (TPE/plasmapheresis)?

Answer:

I use the term “**refractory PANS/PANDAS**” cautiously because there is currently no single universally accepted criterion defining precisely when the condition should be considered refractory.

In practical terms, it generally refers to patients whose symptoms persist or repeatedly recur despite appropriate treatment of identified triggers and the neuroimmune process.

With regard to **therapeutic plasma exchange (TPE), or plasmapheresis**, timing is an important consideration.

According to our clinical observations, plasmapheresis may be particularly effective during the early stages of disease when an active antibody-mediated process is suspected. The rationale is that plasma exchange physically removes circulating antibodies, immune complexes, and other potentially pathological plasma factors.

For this reason, I do not believe that plasmapheresis should be viewed exclusively as a “last-line” treatment after many years of disease. In an appropriately selected patient, the timing of the procedure may be critically important.

At the same time, it is a significant medical intervention requiring careful monitoring. Plasma exchange can reduce not only pathological antibodies but also normal immunoglobulins and other plasma components. This can temporarily weaken humoral immune protection and potentially increase susceptibility to infection. Immunological parameters and the patient's overall condition therefore need to be monitored.

There is another very important practical consideration that is sometimes overlooked: **plasmapheresis can alter the plasma concentration of certain medications**, particularly drugs that are highly protein-bound or have a relatively small volume of distribution.

This is especially important in children receiving **antiepileptic or psychiatric medications**. During a course of plasma exchange, the pharmacokinetic characteristics of each medication should be considered in advance, the timing of medication administration should be coordinated with the procedure, and, where appropriate, therapeutic drug monitoring should be considered for drugs with a narrow therapeutic range. Not all medications are removed by plasma exchange to the same extent.

Plasmapheresis is therefore not simply a procedure for “cleaning the blood.” It is an active intervention targeting the humoral component of the immune process and may be effective in appropriately selected patients, particularly at an earlier stage of disease.

It should be performed in a specialized center, with monitoring of immune status and careful consideration of all concomitant medications.

22. What is the role of biologic therapies or monoclonal antibodies in severe or refractory cases? Under what circumstances might treatments such as rituximab, anti-TNF therapies, IL-6 blockade, or other targeted immunological therapies be considered?

Answer:

Rituximab is not standard therapy for every child with PANS/PANDAS. In protocols and clinical recommendations from specialized expert groups, it is considered primarily in **severe, relapsing, or chronic disease when the clinical presentation and investigation results provide sufficient evidence to suspect an active immune-mediated process**.

Appropriate patient selection is crucial. The decision to use rituximab should not be based on a single positive test, the level of an individual antibody, or simply on the formal diagnosis of PANS/PANDAS.

A comprehensive clinical assessment is required, including disease severity, degree of functional impairment, pattern of disease—acute, relapsing, chronic-static, or progressive—the frequency and severity of exacerbations, objective evidence of an inflammatory or autoimmune process, and response to previous immunomodulatory therapy.

PANS Research Consortium recommendations consider rituximab, in particular, in patients with moderate-to-severe functional impairment, evidence of inflammation or autoimmunity, and objective evidence of organic brain involvement, especially when a previous response to immunomodulatory treatment has been demonstrated. In relapsing disease, an additional consideration may be failure to return fully to the previous functional baseline after successive exacerbations.

Understanding the mechanism of rituximab is important when determining its place in therapy. Rituximab is a monoclonal antibody directed against **CD20**, resulting in B-cell depletion. Its strongest clinical rationale therefore exists when there are reasons to believe that B-cell activity and antibody-mediated mechanisms play a meaningful role in maintaining the pathological process.

Before treatment, appropriate infectious and immunological screening is required. Immunoglobulin levels and B-cell status should be evaluated, and particular attention should be paid to infections that may reactivate during B-cell-depleting therapy, especially **hepatitis B**.

Following rituximab treatment, assessment should not focus solely on laboratory evidence of B-cell depletion. **The primary measure of efficacy should remain the child's clinical course:** reduction in obsessive-compulsive symptoms, tics, anxiety, emotional lability, and other manifestations; restoration of sleep and eating behavior; improvement in learning and everyday functioning; and reduction in the frequency and severity of subsequent exacerbations.

The timing of outcome assessment is also important. Rituximab rapidly reduces CD20-positive B cells, but the clinical effect may develop considerably more slowly. In chronic or refractory immune-mediated disease, meaningful clinical improvement may take several months to become apparent.

Thus, **rituximab is not a treatment for the diagnostic label of PANS/PANDAS itself. It is a targeted immune therapy for appropriately selected patients in whom the clinical phenotype and comprehensive investigation support an immune-mediated disease mechanism.**

23. Do you believe we are moving toward more personalized treatment guided by the child's immunological profile — for example cytokines, immunophenotyping, B/T/NK-cell populations, and autoantibodies? And what role might genetic susceptibility and HLA profiles play?

Answer:

I believe this is one of the most promising directions for the future.

PANS is most likely not a single biologically homogeneous disease. Two children with apparently identical clinical symptoms may have different underlying mechanisms.

For this reason, I am interested not only in the diagnosis but also in the **immune phenotype:** immunoglobulins, B, T, and NK cells, selected cytokine profiles, autoantibodies, and other markers—provided that testing has a specific clinical purpose.

Genetics may also be important. Variants in genes regulating innate and adaptive immune responses, complement, interferon pathways, and HLA may potentially help explain why one child recovers completely after an infection while another develops a persistent neuroimmune phenotype.

However, a substantial proportion of these approaches remains investigational, and families should be informed of this honestly.

24. How much importance do you place on factors that may contribute to ongoing immune dysregulation, such as gastrointestinal dysfunction, mast-cell/allergic mechanisms, metabolic or mitochondrial dysfunction, or environmental exposures including mold and mycotoxins?

Answer:

I try not to view the brain in isolation from the rest of the body. **The nervous, immune, and gastrointestinal systems are closely interconnected**, and we are increasingly recognizing the importance of the gut–immune–brain axis.

A substantial component of the body's immune system is functionally associated with mucosal surfaces, particularly those of the gastrointestinal tract. The intestinal barrier, local immune responses, the microbiota, and microbial metabolites can influence systemic immune processes.

For this reason, gastrointestinal health and the child's nutritional status should not be ignored in the comprehensive management of patients with neuroimmune disorders.

Diet and correction of nutritional status are important components of a comprehensive approach. We should assess the adequacy of the diet, potential nutritional deficiencies, gastrointestinal symptoms, food selectivity, and other factors that may adversely affect the child's overall condition.

Nutraceuticals can also be used as an adjunctive component of treatment, but they should be selected individually according to the child's diet, clinical manifestations, laboratory findings, and specific needs. I do not support prescribing dozens of supplements simultaneously without a clear therapeutic objective and subsequent evaluation of their effects.

When there is objective evidence of gastrointestinal disease, food allergy, mast-cell pathology, metabolic disease, or mitochondrial disease, these conditions should be appropriately diagnosed and treated.

The same caution should be applied to **Candida**. I am strongly opposed to the unjustified use of very high doses or prolonged courses of antifungal medications based solely on nonspecific symptoms or the assumption of “intestinal Candida.” Antifungal treatment should have a clear clinical indication.

A comprehensive approach therefore does not mean searching for a single universal explanation for PANS/PANDAS. It means evaluating the entire organism—the immune system, gastrointestinal tract, nutrition, metabolism, and other coexisting pathological processes.

The objective of dietary and nutritional support is to create optimal conditions for physiological functioning and to correct identified abnormalities. However, these

interventions should not be presented as substitutes for etiological, anti-inflammatory, or immunomodulatory treatment of PANS/PANDAS when such treatment is indicated.

25. After all the children you have evaluated and treated, what do you understand differently about PANS/PANDAS today compared with when you first entered this field? And what message would you most like to give to physicians and families facing this condition?

Answer:

When you first enter this field, it is natural to want to find one test, one infection, or one mechanism that explains everything. But the more children I see, the more convinced I become that **PANS/PANDAS is a much more complex and biologically heterogeneous condition.**

There is no single blood test, antibody, or MRI finding that can establish the diagnosis. Likewise, there is no single universal treatment that will be effective for every child.

The clinical phenotype and its evolution over time remain the most important elements. We need to understand what the child was like before the onset of illness, when the change occurred, how rapidly the symptoms appeared, what preceded them, and how the child's condition subsequently evolved. Only then should we investigate potential infectious, immunological, neurological, genetic, and metabolic factors.

I always listen very carefully to parents, and especially to mothers. There is a unique connection between a mother and her child. A mother sees her child every day and knows their behavior, reactions, sleep, eating patterns, emotions, and even the smallest changes in their functioning. Very often, she senses that something has changed in her child long before those changes become apparent during a brief medical consultation.

That is why when a mother tells me, **“This is not the same child I had a month ago,”** I consider it an extremely important part of the medical history. It does not establish the diagnosis, but it is a signal that a physician should never ignore.

At the same time, we must avoid two extremes. It is wrong to explain every sudden change in a child as purely psychiatric or behavioral. But it is equally wrong to label every behavioral problem as neuroinflammation and initiate intensive immunotherapy without sufficient clinical justification.

Another important message for families is that **treatment requires patience.** Some children may improve relatively quickly, but in complex, longstanding, or relapsing cases, treatment and recovery may take months and sometimes even years.

Recovery is not always linear. There may be periods of significant improvement, plateaus, and subsequent exacerbations, particularly following new infections or other immune

triggers. For this reason, we should not evaluate treatment effectiveness based on a single day or even a single week. We need to assess **the child's clinical trajectory over time**.

My main message to parents is: **do not lose patience, and do not focus only on finding a name for the diagnosis. Work together with your physician to understand what happened to your child and which mechanisms may be maintaining the symptoms.**

And my message to physicians is: **listen to parents, look at the child as a whole, and never ignore a sudden and significant change in a child's condition.**

Finally, we must remain scientifically honest. We have already accumulated a great deal of important knowledge in this field, but many questions remain unanswered.

Our responsibility as physicians is to use the best knowledge available today to help the individual child, carefully evaluate the response to treatment, and at the same time **never present hypotheses as established facts.**