MINI REVIEW ARTICLE

Diagnosis in PANDAS: An Update

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Abstract: Background: The last twenty years have seen major advancements in unraveling the etiology and the identification of biological markers of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococci (PANDAS). However, this body of evidence has not yet been translated into a clinical setting.

Objective: We will review the most important studies to date on PANDAS, emphasizing those whose advances could improve the diagnosis of these disorders. We also suggest the need for updated diagnosis criteria integrating the recent findings from the hereby included studies.

Methods: Consulting the PubMed database, a literature review of the last twenty-one years (between 1998 and 2019) was carried out using the terms “PANDAS” and “pediatric autoimmune neuropsychiatric disorders” in combination with “diagnosis” and “markers”. The search resulted in 175 hits from which we selected clinical cases, original investigations, and clinical reviews.

Results: This review offers a compilation of the most important studies performed to date regarding the clinical presentation and potential biological markers of PANDAS. Moreover, we suggest the refinement of some aspects in the current diagnosis criteria, such as focusing on specific symptoms and the inclusion of neuroimaging and peripheral markers.

Conclusion: The identification of specific biological markers in PANDAS is crucial for its diagnosis and opportune treatment. Future research will determine whether PANDAS require separated diagnostic and therapeutic measures or if it should be included in recently proposed categories such as Pediatric Acute Neuropsychiatric Syndrome (PANS) or Childhood Acute Neuropsychiatric Syndrome (CANS).

Keywords: OCD, tics, streptococcal infection, autoimmune, early-onset OCD, diagnosis, biomarkers.

1. INTRODUCTION

The Obsessive-Compulsive Disorder (OCD) is a heterogeneous psychiatric disorder composed of several subtypes with variable age onset, symptoms, and etiology [1, 2]. Within these subtypes, there is a group of neuropsychiatric disorders characterized by the sudden onset or exacerbation of motor alterations, tics and/or OCD and whose symptoms are temporally associated with a streptococcal infection in pediatric patients [3]. This group of neuropsychiatric disorders has been defined as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococci (PANDAS) [4].

Regardless, it has been hypothesized as a result of an aberrant immune response to streptococcal infection [5].

Such response could lead to a neuroinflammatory process in the basal ganglia of susceptible individuals, triggering motor and behavioral abnormalities [6].

The term PANDAS was coined in 1998 by Swedo et al. [3]; however, the description of symptoms and abnormalities related to this condition has progressed considerably in the last twenty years. These advances, along with the study of etiological mechanisms involved in PANDAS, have led to the identification of promising biomarkers and treatment options.

Further, other diagnostic categories have been proposed in addition to PANDAS in the recent years. Such categories include a wider range of symptoms and etiological agents that have been related to the abrupt onset of neuropsychiatric...
disorders in children, such as the Pediatric Acute Neuropsychiatric Syndrome (PANS) and the Childhood Acute Neuropsychiatric Syndrome (CANS) [7, 8].

However, the classification of PANDAS within those categories may create a more heterogeneous population within the realm of pediatric neuropsychiatric disorders, thus hampering its diagnosis and adequate treatment. Likely, this problem arose from the fallible application of the original diagnostic criteria in the clinical setting [9]. Therefore, updated and refined criteria including the observations made in recent studies could improve the diagnosis of PANDAS.

Concerning the latter, previous reviews have been focused on their clinical presentation [10], diagnostic controversies [11-13], and treatment [6]. In this manuscript, however, we emphasize other areas deserving of more attention and which could be useful in a clinical context, e.g. the detection of specific antibodies and clinical symptoms. Further, we propose the integration of recent advances made in this regard into the original diagnosis criteria of PANDAS. Such addition would entail the translational application of these past studies, potentially improving its diagnosis.

2. MATERIALS AND METHODS

A literature review of the last twenty-one years of research (between 1998 and 2019) was performed using the PubMed database, the search included the following keywords: “PANDAS” and “pediatric autoimmune neuropsychiatric disorders” in combination with the keywords “diagnosis” and “markers”. We chose only the most relevant reports for the history section, extending its period to the last 90 years.

The search resulted in 175 hits from which we selected clinical cases, original investigations, and reviews focused on clinical topics. We did not consider those studies including patients that did not meet the clinical criteria of PANDAS and the articles focused on PANS and/or CANS. A total of 93 articles were selected for the present review.

We classified these studies according to their content in historical reports, clinical descriptions, and studies of potential biological markers. Concerning the section for the latter, we included neuroimaging, peripheral antibodies and susceptibility markers for their potential relevance in the diagnosis of PANDAS.

3. RESULTS

3.1. History

Several cases of patients with tic disorders accompanied by movement and behavioral disorders temporally related to infections have been reported since the turn of the 20th century [13-19]. The subjects presented motor and vocal tics indistinguishable from those observed in patients with Tourette syndrome. Further, a remarkable feature in these described cases was the lacking response to conventional therapy for tics. Instead, the patients only exhibited a noteworthy improvement after the administration of adrenocorticotropic hormone or corticosteroids [20].

In 1995, Allen et al. used the term PITANDs (Pediatric Infection-Triggered, Autoimmune, Neuropsychiatric Disorders) to describe the group of disorders temporally related to an infectious process. Interestingly, viral infections were included within this term as probable triggers of pediatric OCD and motor abnormalities [21].

In 1998, Swedo et al. described the exacerbation of OCD symptoms and/or tics after a streptococcal infection in a sample of 50 children. The term “Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus” (PANDAS) was proposed for the first time to address this syndrome. Unlike the term “PITANDs”, “PANDAS” only comprised the cases related to Streptococcus as a probable cause of the symptoms [3].

However, other diagnostic categories have been recently proposed, such as PANS and CANS, due to the difficulty to establish a temporal and causal relationship between streptococcal infection and the onset of neuropsychiatric symptoms [7, 8, 22], especially because the identification of the precipitating factor is not required in these clinical entities [8].

PANS and CANS comprise a broad spectrum of neuropsychiatric conditions with similar symptoms that are probably the result of different disease mechanisms and multiple etiologies [23]. Therefore, unraveling the etiology of these disorders will prove useful in the development of specific treatments and the crucial understanding of the subtypes expected within PANS and CANS.

3.2. Diagnostic Criteria

In 1998, Swedo et al. [3] provided the first comprehensive description of PANDAS. In addition, they also proposed guidelines for its diagnosis using the following criteria: 1) OCD and/or tics, 2) Pediatric onset, 3) Acute onset and episodic course, 4) Association with group A beta-hemolytic streptococcal (GABHS) infections, and 5) Association with Neurological Abnormalities.

However, there is some controversy regarding the low specificity of these criteria. Further, there is a considerable overlap between the symptoms presented by patients with PANDAS and those observed in patients with other motor disorders, such as Tourette syndrome and Sydenham’s chorea (SC). Therefore, a clear distinction between such disorders is critical, as their treatment is different [24].

3.2.1. OCD and/or Tics

The symptoms for OCD and/or tics are considered as cardinal manifestations in PANDAS; therefore, they have become essential for its diagnosis. Interestingly, such symptoms are very common during childhood, as several disorders might cause tics in pediatric patients, such as systemic lupus erythematosus, encephalomyelitis, intoxication, thyrotoxicosis, Wilson’s disease, Attention Deficit Hyperactivity Disorder (ADHD), anxiety disorders, among other neurological disorders [25]. Less than 20% of tics observed in pediatric patients are caused by PANDAS, so it stands to reason that they are now considered as an exclusion diagnosis [26].
However, Swedo’s cohort presented an equal prevalence for tics and OCD as a primary diagnosis, where the most prevalent OCD symptoms were phobia, contamination, risk of harm to self or others, and somatic concerns. Moreover, there were clear differences in OCD symptoms according to gender: girls presented more washing rituals, while boys presented greater verification rituals, tics, and aggressive compulsions [4]. Notably, facial movements and blinking are the most frequent tics in PANDAS [25].

A recent study by Gamucci et al. [27] reported some differences in the clinical presentation of patients with PANDAS in comparison with patients with PANS or SC. These differences were manifested by obsessive and somatic symptoms, and behavioral regression, thus highlighting the existence of symptomatic differences between conditions previously considered as similar. Further exploring these contrasting symptoms could be helpful in a clinical setting.

### 3.2.2. Pediatric Onset

PANDAS are defined as a pre-pubertal disorder, with recent studies reporting an earlier age of onset in comparison to SC or PANS [24, 27, 28]. Individual variations in the age of onset and its implications in the course and prognosis of the disease have not been explored in PANDAS. However, considering its relevance among auto-immune disorders, this factor is worthy of future study [29].

### 3.2.3. Acute Onset and Episodic Course

In general, typical symptoms such as tics and OCD have a gradual onset. However, patients with PANDAS usually present an abrupt onset instead. It must be highlighted that this occurrence is not specific to PANDAS only, as this sudden onset has also been observed in patients with Tourette syndrome. Further, not all patients with PANDAS display an acute symptom onset, which may vary from ten days to several months [9, 30, 31].

### 3.2.4. Association with GABHS Infections

Probably the most debated aspect within the definition of PANDAS, the association with group A beta-hemolytic streptococcal infections has been controversial due to the uncertain relationship between both events. Further, we should be aware that both, streptococcal pharyngitis and tic disorders, are very common in pediatric patients; thus, establishing a clear link between both events has become challenging.

Immunization against GABHS is known to induce motor and behavioral alterations in mice [32, 33]; however, the administration of corticosterone counteracts these effects [34]. These observations concur with the hypothesis that GABHS infections might induce an auto-immune response in vulnerable individuals, ultimately leading to motor and behavioral disorders. Further, the amelioration of these symptoms after the administration of immunomodulators supports the hypothesis of an auto-immune etiology in PANDAS.

Some human epidemiology studies have suggested the association between streptococcal infections and the appearance or exacerbation of motor disorders [30], OCD and/or tics [35, 36]. In comparison to healthy control subjects, patients with tics, OCD and Tourette syndrome were 2.22 times more likely to have been afflicted with at least one streptococcal infection in the three months prior to symptom onset [37]. However, other studies have reached contradicting conclusions in this regard [38, 39].

A recently conducted meta-analysis failed to detect a greater exacerbation ratio in neuropsychiatric symptoms in temporal proximity with streptococcal infection. Regardless, patients with PANDAS had an increased risk of exacerbated neuropsychiatric symptoms in comparison to healthy control subjects [40]. It is possible that the use of a larger population in future studies will clarify the link between GABHS infections and the onset of neuropsychiatric symptoms.

Within a clinical setting, pharyngeal cultures and streptococcal antibody titers are the only available methods in the diagnosis of GABHS infections. However, a pharyngeal culture is unable to distinguish between an active infection from a carrier state; therefore, it is an impractical method in the detection of Streptococci as a triggering event in PANDAS [41].

The titration of Streptococcal antibodies is the most accurate serological method in the diagnosis of previous streptococcal infections; further, the simultaneous detection of two or more antibodies increases the sensitivity of this test [42]. This approach could be particularly useful in the diagnosis of PANDAS, since greater titers of anti-enulose, anti-neural and anti-streptococcal antibodies could be useful in associating *Streptococcus* as a possible etiologic agent in patients with early-onset OCD [43].

### 3.2.5. Association with Neurological Abnormalities

Choreiform movements have been included within the neurological abnormalities observed in patients with PANDAS; however, these can be confused with choreatic movements. Therefore, the accurate description of their main differences is needed to prevent this confusion.

The choreiform movements displayed by patients with PANDAS are seemingly provoked by physical examination, although without causing functional disability [44, 45]. These movements are manifested as rapid spasms or torsion movements of the fingers, wrists, arms, elbows, and shoulders [3]. These choreiform movements are also observed in healthy minors and children with viral infections; therefore, they are not specific to PANDAS [38, 46]. Regardless, these movements might be helpful in the differential diagnosis of tics and OCD symptoms in the context of a streptococcal infection.

On the other hand, choreatic movements are described as intentional and usually result in functional disability. These movements have been typically observed in SC, which is also characterized by dysarthria and hypotonia [47]. Therefore, the detection of these abnormalities and their associated characteristics during physical examination, along with other clinical indicators, could be of assistance in the differential diagnosis of movement disorders.

In addition to motor abnormalities, several neuropsychiatric symptoms have also been described in patients...
with PANDAS, such as writing impairment, decreased motor skills, hyperactivity, lack of concentration, learning disabilities, attention deficit hyperactivity disorder, sleep disorders, language disorders, psychomotor disorders, urinary urgency, nocturnal enuresis, emotional liability, personality changes, and separation anxiety [48-51].

3.3. Neuroimaging in PANDAS

It is reasonable to hypothesize that patients with PANDAS could present neuroanatomical abnormalities due to its neuropsychiatric symptomatology and probable autoimmune etiology. It is possible that such anatomical changes could be caused by neuroinflammation or antibody-induced damage.

Most neuroimaging studies concerning PANDAS have been focused on basal ganglia because of its crucial role in movement control and for being the target of autoimmune antibodies found in the patients’ serum. These MRI studies have reported the enlargement of the basal ganglia in patients with PANDAS [52-54]. Interestingly, the volume of this group of structures was diminished after plasmapheresis and treatment with lorazepam [52, 54].

The relevance of basal ganglia in PANDAS has been evidenced in functional neuroimaging studies as well. Citak et al. [55] identified bilateral hypoperfusion in both thalamus and striatum, which was interpreted as a probable inflammatory process. Positron emission tomography (PET) studies have reported bilaterally inflamed areas in the caudate and lentiform nuclei of patients with PANDAS; unlike patients with Tourette’s, where only the caudate nucleus was inflamed [56]. Given the similarities between both disorders, these events could represent a pivotal difference with Tourette syndrome.

The neuroanatomical characteristics of patients with PANDAS are different from those reported in other OCD subtypes, in which significant volumetric differences in basal ganglia have not been detected [57]. However, increased basal ganglia volume is similar in subjects with SC [58]. Therefore, this characteristic could not be useful in discriminating between both disorders.

Besides their potential to unravel pathophysiological mechanisms and to identify structural and functional abnormalities, neuroimaging studies might also be useful as diagnostic tools. In this regard, a multivariate pattern analysis (MVPA) demonstrated that the abnormalities in the gray/white matter patterns in the cortex, subcortex and cerebellum allowed the classification of patients with PANDAS with an accuracy of 75% and 61%, respectively [59]. Therefore, multivariate tools might improve its diagnosis through their high sensitivity and specificity; moreover, they are particularly useful on a personalized level, which is highly advantageous in a clinical setting [60]. A graphical summary regarding neuroimaging studies performed on PANDAS is shown in Fig. (I).

Undoubtedly, future neuroimaging studies should give serious consideration to whole brain analyses in patients with PANDAS, since structure abnormalities unrelated to movement could explain the neuropsychiatric symptoms observed in these patients.

3.4. Peripheral Antibodies

The production of auto-antibodies in response to streptococcal infections has been proposed as a pathophysiological mechanism of SC. In support of this hypothesis, it has been suggested that the auto-antibodies produced after streptococcal infection cross the blood-brain barrier and react against the neuronal surface, especially against basal ganglia neurons, thus causing motor dysfunction [61].

A similar mechanism has been proposed for PANDAS, given its symptomatic similarities with SC (e.g. sudden onset, motor alterations, and probable association GABHS infections). Therefore, the identification of auto-antibodies targeting neural components in the serum of patients with PANDAS support the antibody hypothesis [62].

Furthermore, the identification of neural auto-antibodies in peripheral blood would represent a non-invasive approach to determine the markers involved in central nervous system processes. Some of the antibodies identified in patients with PANDAS are related to relevant neurotransmitters systems, i.e. dopaminergic signaling. Serum samples from patients with PANDAS exhibit higher titers of dopamine D1 and D2 receptor antibodies, whereas the serum obtained from patients with SC reacts against the dopamine D1 receptor only [63]. These observations suggest that the exposure to streptococcal antigens could affect the dopamine pathways and thus result in movement and behavior abnormalities.

The elevated levels of anti-dopamine receptors in patients with PANDAS could lead to the activation of calmodulin-dependent protein kinase [64, 65], which is involved in functions such as learning, memory and cell development [64]; however, its role in PANDAS and OCD is unclear. Further, its activation could be associated with the pathological mechanisms causing neuropsychiatric symptoms in patients with PANDAS.

Increased titers of anti-basal ganglia antibodies have been reported in subjects with PANDAS when compared to control subjects [66, 67]. The presence of these antibodies is consistent with the motor abnormalities observed in these patients; however, these elevated titers are not exclusive of PANDAS, which have also been found in patients with disorders such as non-streptococci related OCD, Tourette syndrome, motor and/or vocal tics, and chorea SC [68, 69].

Furthermore, antibodies targeting the cholinergic interneurons have been identified in the serum of patients with PANDAS. These cells have an active role in modulating the activity of other neuronal types in the basal ganglia. Frick et al. [70] suggest that the deposition of such antibodies could alter the function of cholinergic interneurons, causing the symptoms displayed by patients with PANDAS. A graphical summary of the peripheral antibodies identified in PANDAS is shown in Fig. (2).

The following neuronal glycolytic enzymes are among some of the antigens that could trigger an autoimmune response in patients with PANDAS: aldolase C, neuronal specific enolase, non-neuronal enolase, and pyruvate kinase. These antigens have been found in intracellular locations and over the neural surface. This finding supports the hypothesis...
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of cross-reactivity in PANDAS since group A streptococci express glycolytic enzymes on its membrane [71].

Therefore, evaluating the cross-reactivity to streptococcal antigens is key in determining the etiology of PANDAS, especially since molecular mimicry has been proposed as an initiating mechanism of the auto-immune response shown by these patients. Although the hypothesis that PANDAS is an antibody-mediated disorder is plausible, other mechanisms, such as the presence of superantigens or alterations in cellular immunity, have been little explored [71]. The consideration and study of other pathophysiological mechanisms should not be neglected in PANDAS, as these mechanisms are not mutually exclusive and might explain the broad spectrum of symptoms presented by these patients.

The identification of self-epitopes is crucial for the implementation of antigen-specific therapy. In addition, their characterization would improve the understanding of this pathology in a valuable way by improving its prognosis since the nature of these antigens may influence the response to treatment [72]. Another aspect that deserves attention is the correlation between the antibody titers and symptomatology; as this could explain their role in the etiology of PANDAS, else their presence could be considered an epiphenomenon.

3.5. Immune System Abnormalities

Most patients with streptococcal infections do not develop PANDAS; therefore, a predisposition towards its development has been hypothesized. PANDAS is a pathology with probable auto-immune etiology where a series of diverse antibodies have been identified. Thereby, it is reasonable to postulate that patients with PANDAS may have immune anomalies augmenting their predisposition to an abnormal immune response and the appearance of neuropsychiatric disorders.

In this regard, the lymphocyte surface marker D8/17 has been proposed as a susceptibility factor. Its expression has been identified with greater frequency in children with streptococcus-related disorders, such as rheumatic fever and SC, as well as in patients with tics [73, 74].

This marker has also been detected in patients with non-GABHS related OCD, suggesting its involvement in the vulnerability to OCD independently of streptococcal infections [75]. The detection of this marker can be easily achieved in a clinical setting through flow cytometry in combination with immunofluorescence assays [76]. Regardless, no clear correlation has been established

![Fig. (1). Graphical summary of neuroimaging studies performed on patients with PANDAS.](image-url)
between D8/17 expression and OCD symptoms and/or tics, nor to their exacerbation [77-79]. Accordingly, the compiled evidence so far does not justify its clinical use.

On the other hand, the 308 G/A polymorphism in the TNF-α promoter region has been proposed as another candidate marker in the predisposition towards PANDAS. This polymorphism has been found with greater frequency in patients with PANDAS than in healthy controls [80]. However, the predisposition towards an autoimmune disease is the result of multiple polymorphisms in the genes involved with immune function; therefore, additional polymorphisms could still be identified in patients with PANDAS [81].

Only few studies have evaluated the abnormalities predisposing these individuals to an altered immune response after streptococcal infection. Concerning humoral immunity, patients with PANDAS do not show alterations in the number of tonsillar B-cells nor in the expression of B-cell activation factors [82]. Unfortunately, there is only one available report on the elevated levels of alpha and eotaxin-3, and the decreased levels of IL-8, IL-10, IL-17a, IFN-γ, IL-10, and IL-12 in these patients when compared against those that did not develop motor or neuropsychiatric disorders after a streptococcal infection [83].

B cells are involved in several processes that could start an autoimmune response, such as B-cell signaling, tolerance mechanisms, and antigen presentation [84, 85]. Therefore, the study of other immune mechanisms could reveal other alterations in this cell lineage in patients with PANDAS.

Regarding T cells, a lower number of regulatory T cells has been observed in children with Tourette syndrome or PANDAS, supporting the hypothesis of an autoimmune process in both disorders [86]. Future studies focused in cell-mediated immunity, as could be the counting and functional profiling of other T lymphocyte populations in patients with PANDAS, could explain the cellular response to Streptococci and thus determine whether an abnormal pathway could contribute to the pathogenesis of PANDAS.

Due to their involvement in the immune function, Vitamin D and the parathyroid hormone have also been

**Fig. (2).** Graphical summary of antibodies detected in serum of patients with PANDAS.
studied in relation to PANDAS [87, 88]. Interestingly, the levels of these molecules have been correlated with symptom severity, although they seem to have no effect on anti-streptolysin O titers [87]. Their correlation with symptom severity is particularly relevant, suggesting the potential usefulness of these molecules in a clinical setting and thus encouraging further study to unravel their involvement in the pathophysiology of PANDAS.

4. DISCUSSION

4.1. Diagnosis Criteria

In 1998 Swedo et al. proposed the original criteria for the diagnosis of PANDAS [3]. Since then, our understanding of PANDAS has advanced notably. Therefore, as in all scientific fields, it is necessary to translate the most recent advances made in PANDAS into a clinical setting, being this translational process the ultimate end of the research.

In our opinion, it would be convenient to integrate the knowledge generated in recent years to the improvement of diagnosis criteria, the detection of PANDAS, and its opportune treatment. Some of the elements that could strengthen this diagnosis criteria are as follows:

4.1.1. OCD and/or Tics

There is a high prevalence of these symptoms in pediatric patients, which are associated with multiple etiologies and have become a major criterion in the diagnosis of PANDAS. Therefore, it would be reasonable to determine whether the patients with PANDAS show specific characteristics regarding these symptoms, such as higher prevalence in certain compulsions or obsessions that could set them apart from patients with similar disorders.

In this regard, Swedo et al. [4] provided valuable information by describing these characteristics in a group of patients with PANDAS. However, additional studies with larger populations are still needed before establishing an in-depth symptom profile in patients with PANDAS. Further, deciphering the factors influencing its presentation and/or severity is essential to identify which of these factors might modify the manifestation of PANDAS.

4.1.2. Pediatric Onset

It should be considered that PANDAS are not the only disease with an onset prior to adolescence and that typical tic disorders also occur in pre-pubertal patients. With this in mind, this criterion turns out to be inaccurate and impractical when seeking to differentiate between the tics caused by PANDAS or by other etiologies [89].

It would be a worthwhile pursuit to determine any differences regarding the age of onset between PANDAS and other motor disorders, such as those observed in SC [24, 27, 28]. If such differences could be established, a more precise lapse could be proposed for this criterion.

PANDAS, by definition, is a pediatric disorder; however, it has not been ruled out that some OCD/tics symptoms may also be present in adults as a direct result of a Streptococcal infection [90]. Therefore, identifying the predisposition biomarkers might be more pertinent than the definition of age boundaries.

4.1.3. Acute Onset and Episodic Course

The notion of an ‘abrupt’ onset is not well defined and may, therefore, be subject to relative interpretation [24]. Thus, delimiting a more precise lapse in the symptoms’ appearance could resolve whether the inclusion of this criterion is useful in the classification of PANDAS, setting an adequate time frame for this criterion if such were the case.

4.1.4. Association with GABHS Infection

It is particularly difficult to establish a temporal association between a Streptococcal infection and the onset or exacerbation of PANDAS symptoms. Hence that the simultaneous detection of two or more antibodies represents a practical and viable option, having demonstrated higher sensitivity in comparison with single measures.

In addition, the inclusion of antibody titration in the diagnosis of PANDAS would provide specific markers and improve the translational application of current clinical criteria. Such inclusion could upgrade the diagnosis standard significantly.

4.1.5. Association with Neurological Abnormalities

Including a clearer description of the neurological abnormalities induced at the time of physical examination may prove beneficial in a differential diagnosis. PANDAS have a complex identity; therefore, the specific search for certain signs during physical examination might be useful in a clinical setting.

As we discussed in previous paragraphs, the current criteria for the diagnosis of PANDAS are vague and unspecific. In addition, approximately 76% of patients diagnosed with PANDAS are not in strict compliance with the diagnostic criteria [91]. In addition to OCD and/or tics, other neuropsychiatric symptoms previously described in patients with PANDAS should be considered, such as writing impairment, enuresis, lack of concentration, etc. Moreover, due to the differences in clinical presentation between patients with PANS, PANDAS, and SC [27], it might prove worthwhile to further identify these disparities, thus allowing the accurate discrimination between patients with similar symptoms.

Furthermore, it is important to evaluate the prevalence of neuropsychiatric abnormalities in subjects with PANDAS so that a clearer understanding of the broad range of associated symptoms might be possible.

4.2. Inclusion of Biomarkers

In addition to Streptococcal antibodies, neural antibodies have also been detected in patients with PANDAS; therefore, evaluating their sensitivity and specificity, combined with Streptococcal antibodies or by themselves, could be included in its diagnosis (Fig. 2).

Further, antibody titration methods should be standardized since variations in their measurement may lead to a difficult interpretation and poor reproducibility in
subsequent studies [92]. Regardless, their detection is a promising approach due to its relatively easy methodology and practicality in a clinical setting.

On the other hand, neuroimaging tools have shown a consistent alteration of the basal ganglia. Therefore, we can infer its correlation to the symptoms displayed by the patients with this OCD subtype. However, this type of alterations is present in several disorders. Moreover, most of the neuroimaging studies have been solely focused in basal ganglia, so it is not surprising that the reported alterations are limited to this region.

Evaluating the anatomical characteristics of other structures involved in the movement, such as the cerebellum and the primary motor cortex, might be helpful in the identification of structural and functional abnormalities in PANDAS. In this regard, the use of novel neuroimaging techniques may shed light in focal pathophysiological processes. Further, since the presence of an inflammatory process has been supported by several studies [54, 56, 57], neuroimaging techniques targeting neuroinflammation could provide valuable information concerning the cells and molecules involved in the immune response to this disorder [93].

Future studies must consider the inclusion of adequate control groups and patients with other tic disorders in order to identify specific characteristics in the patients with PANDAS, thus allowing an accurate discrimination between patients with similar disorders.

In our opinion, potential neuroimaging markers should be further explored and validated prior to their inclusion in the diagnosis criteria of PANDAS. The same should be applied to susceptibility markers, among which Vitamin D and the parathyroid hormone are noteworthy due to their correlation with the observed clinical scores [87]. The validation of these biomarkers in other populations, as well as determining their role in PANDAS, could set the basis for their use in a clinical setting.

4.3. Current & Future Development

New strategies for the identification of specific clinical signs and markers are imperative for the diagnosis of PANDAS. Highly specific and sensitive markers will allow the opportune classification of these patients without the need to point at GABHS as a triggering agent for each individual case, which is extremely difficult in clinical practice.

Although some authors consider PANDAS within PANS, we consider that the former should be studied as a separate entity. In this manner, future studies addressing the characterization of this disorder will likely benefit from homogeneous samples and their results will be interpreted correctly.

Descriptive studies and the identification of candidate etiological agents for other disorders comprised under PANS or CANS are crucial in this understanding, as well as for the design of preventive and therapeutic measures. Other than Streptococcus, the recognition of immune or infectious factors as triggers of neuropsychiatric symptoms will provide enhanced knowledge about the pathogenesis of OCD, improving the identification of patient subgroups, whom will benefit from a more focused treatment.

CONCLUSION

Despite the major advances made on the subject of PANDAS, further research is needed at multiple levels, such as epidemiology, comorbidity profiles, and biological markers. And though this lack of information is somewhat limiting, it also pushes for a more detailed characterization of PANDAS and other neuropsychiatric disorders.

The continuous study of PANDAS is essential for its understanding. Moreover, the identification of specific markers is also crucial for its improved diagnosis and opportune treatment. The need for further studies addressing the interaction between pediatric neuropsychiatric conditions and infectious agents cannot be understated in the establishment of diagnostic and therapeutic measures, which might as well be different than those recommended for broader diagnostic categories such as PANS and CANS.
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