REVIEW

Post infectious CNS disorders: towards a unified approach

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Abstract The spectrum of post infectious (PI) central nervous system (CNS) conditions includes a range of grey and white-matter disorders which can occur after viral or bacterial infections or in response to vaccinations. The clinical, radiological and immunological phenomenology raises a number of issues regarding the nature of immune-mediated CNS abnormalities, their etiology, pathogenesis and therapy. Here we focus on crucial issues pertaining to pathogenesis and aim to identify where current knowledge is insufficient in order to suggest future avenues of clinical and experimental research that may help to devise optimal therapy for these conditions.

Keywords Post infectious · Infections · Central nervous system · Demyelination

Introduction

Neurological conditions described as being "post-infectious" may occur either after an active infection or in response to a vaccination. While most pathogens can cause a disease during the infective process, certain agents are also capable of producing tissue damage by post-infectious (PI) mechanisms, which may make the diagnosis of the disorder, and thus determination of the therapy, difficult. An example is *mycoplasma pneumoniae* which can damage the central nervous system (CNS) through direct invasion [1], via a neurotoxin [2], or by immune-mediated mechanism [3].

Although, ideally, the term post-infectious should exclude scenarios where the infective pathogen remains in the tissue, the mere presence of the organism within the host does not exclude a post-infectious mechanism. The distinction is more than semantic, as infectious and PI conditions will often prompt completely different treatment strategies. Thus, it might be more appropriate to use the term "para-infectious" to denote mechanisms not caused by an active infectious process, irrespective of the temporal relationship to infection. In practice, separation of infectious from PI processes is challenging, but conceptually, infectious processes depend on the continued presence of viable micro-organisms and should be treated with *anti-microbial therapy*, while PI processes ought to be blocked by *inhibition of the involved host processes*.

Rather than provide a comprehensive update of all PI conditions affecting the CNS (Table 1), we aim: (1) to focus on their pathogenesis and, (2) to suggest future avenues of clinical and experimental research, especially where current knowledge is insufficient, that may help elucidate the natural history, pathogenesis and optimal therapy in these conditions.

When to suspect a PI neurological condition (Table 2)

A condition may be suspected of having a PI etiology when neurological symptoms and signs compatible with an acute immune-mediated condition appear following recovery

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Table 1 Post infectious CNS conditions

Grey-matter

  Sydenham's chorea

  Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

  Encephalitis lethargica

  Post infectious dystonia

White-matter

  Acute disseminated encephalomyelitis (ADEM)

  Post infectious transverse myelitis

  Post infectious optic neuritis

Table 2 Proposed clinical criteria to suspect a post infectious disorder

Major

  Proven antecedent exposure: either an overt febrile illness or receipt of a vaccination.

  Temporal relationship between pathogen or vaccine exposure

  Direct or indirect evidence to support an immune-mediated mechanism according to the criteria proposed by Rose and Bona [4].

Minor

  Inability to identify the pathogen in the tissue during tissue damage[a]

  Proof that the infective pathogen is not directly cytotoxic to the CNS at the time of the disease despite being detectable in the tissue during tissue damage

We suggest that a condition should be regarded as "definitely PI" if all three major and one minor criteria are met, and "probably PI" if all three major criteria are present without either of the minor criteria.

[a] Although CNS samples are seldom available for a particular patient, the consistent failure to detect a pathogen in the condition in general would be supportive of a PI disorder.

from an infection/vaccination, or if there is evidence of active neurological disease, following full resolution of infection. Additional supportive features include: (1) inability to identify the pathogen in the tissue during the appearance of new neurological disturbances; (2) neurological damage is not known to be caused by the relevant pathogen; (3) evidence of an immune-mediated mechanism according to the criteria proposed by Rose and Bona [4], adapted from the Koch–Witebsky criteria for autoimmunity [5]. These also include: induction of the condition through passive transfer of the autoantibody, reproduction of the disorder in an appropriate animal model and a favorable response to immunotherapy. We suggest using these features as criteria to diagnose a PI condition (Table 2).

It should be remembered, however, that even when a "new" neurological abnormality comes to light, it may reflect damage which occurred during the acute infection but went previously unnoticed, or may be due to infections (such as syphilis) that have a polyphasic or a chronic clinical course [6].

What determines the tissue specificity of the immunological attack?

Tissue specificity is a general feature of PI immune-mediated conditions. *Campylobacter jejuni* is associated with Guillain–Barré syndrome, while Streptococcus is implicated in several conditions involving the basal ganglia (BG).

The immune-system is primed to attack antigens labeled as "foreign", whilst tolerating "self". The attack of "self antigens" could be due to faulty recognition on the part of the immune-system, alteration of self antigens that are no longer recognized as such, or exposure of self antigens that are usually shielded from the immune-system [7].

Several factors may determine an infective agent's ability to induce a PI condition in a particular tissue.

1. The organ and cellular specificity of the infectious process, such as when viral infections are dependent on cell surface receptors (e.g. autoimmune hepatitis due to hepatitis A virus [8]).
2. Structural similarity between pathogens and self antigens, the prerequisite for "molecular mimicry". This probably underlies the propensity of Streptococcus to trigger conditions affecting the BG [9].
3. The function of the organ. The filtration process through glomeruli may lead to deposition of immune complexes in the kidney and immune-mediated glomerulonephritis [10].
4. The nature of the pathogen. Cytomegalovirus (CMV) is associated with several dysimmune disorders (systemic lupus erythematosis, Guillain–Barré syndrome) attributed in part to its ability to manipulate the immune-system.
5. The accessibility of the organ to agents of the immune-system activated by the infection. This is highly pertinent to the CNS and the blood–brain barrier (BBB) [11].

However, the restricted accessibility of the CNS and the lack of locally generated immune responses require additional explanation when CNS PI conditions take place. These may eventually also be due to one of the following:

a. Cross-reactive epitopes that are accessible solely on CNS structures.
b. Generation of auto-reactive cells/antibodies that occur and are held within the CNS and the BBB.

Basal ganglia and post streptococcal CNS symptomatology

Probably the best example of a PI condition that affects a specific brain structure is that of BG dysfunction following streptococcal infection. The BG are affected in several disorders that are either proven to follow group A beta-hemolytic Streptococcus (GABHS) or suspected to be post-streptococcal conditions. Their comparative features are summarized in Table 3.

Sydenham's chorea (SC)

SC typically occurs 1–6 months following GABHS infection, lasts several months and resolves spontaneously. Recurrences are not rare [12]. The diagnosis of SC is clinical: although antistreptolysin-O titres (ASOT) are usually raised, there is no definitive confirmatory laboratory test, so the primary goal of paraclinical studies is to exclude other causes. There is radiological and histological evidence of selective BG inflammatory, but not infectious, involvement [13].

The therapeutic response to IVIg and plasmapheresis is consistent with an antibody-mediated process [9]. The antibodies present in SC patients bind to both streptococcal carbohydrate molecules and brain ganglioside auto-antigens [9], are capable of altering intracellular activity in the absence of cytotoxicity and may alter CaM kinase activity to increase the release of dopamine, the main neurotransmitter implicated in hyperkinetic movement disorders [9, 14].

Familial clustering [12] and the identification of a recessively inherited B-cell marker [15] suggests that a genetic background may determine susceptibility.

Dystonia associated with anti-BG antibodies

Anti-BG antibodies were detected in 65% of patients with atypical movement disorders, primarily dystonia [16]. A preceding streptococcal infection is often present, suggesting that it may be an extension of the SC phenotype.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

PANDAS is a recently defined and still controversial entity describing a Streptococcus-associated childhood tic or obsessive–compulsive disorder with an acute or episodic course [17] where ASOT titers are often raised. Current techniques cannot separate PANDAS patients from controls [18] and passive transfer of PANDAS serum does not affect behavior or movement in rodents [19]. Is PANDAS a separate nosological entity from SC? It seems that the SC/PANDAS spectrum is relatively homogenous, clinically,

paraclinically and probably pathogenetically (Table 3). The fact that adults may be afflicted by both conditions would argue against separating the pediatric and the adult entities. If the evidence for anti-BG antibody mediation and GABHS cross-reactivity in PANDAS becomes as convincing as in SC, there may be a rationale in lumping the GABHS-associated conditions together under the new term PANAMAS (pediatric/adult neuropsychiatric and movement disorders associated with Streptococci).

Encephalitis lethargica (EL)

EL is an acute or subacute condition characterized by lethargy, sleep disturbance and an extrapyramidal movement disorder, often accompanied by ophthalmoplegia, oculogyric crises and neuropsychiatric disturbances [20]. First described by von Economo in 1917 in association with the Spanish influenza epidemic, Von Economo [21] himself reported a similar disorder in dogs vaccinated against Streptococcus. More recently, it has been suggested that EL may also be a PI post streptococcal condition [20] and therefore may belong to the PANAMAS spectrum.

These entities and the range and variety of their neurological symptomatologies raise several issues.

Who develops a disease after infection?

Genetic background is important in setting the stage for immune-mediated conditions [22]. Markers of susceptibility, most notably the presence of the D8/17 B cell marker, were found in SC and PANDAS [15], and it was found that familial clustering occurs [23]. Moreover, PANDAS may take place without evidence of prior streptococcal exposure, and we have shown that chorea occurs in patients with previous SC in the absence of streptococcal re-infection [12]. Additional possibilities include a congenital structural susceptibility unique to the individual that may enable cross-reactivity with pathogen antigens, or a "double hit process" where a previously acquired change in BG antigenic structure renders the tissue susceptible to an immune response following infection.

If the tissue and the pathogen are the same, why is there clinical variation?

The various parameters that may influence the severity of the clinical disorder (detailed in Table 4) can be categorized into genetic differences, environmental factors and pathogen variability. In addition, there are factors related to the lesion itself that may impact the presentation and course of the disease:

Table 3 Comparative features of post infectious disorders affecting the basal ganglia

	Movement disorder	Psychiatric manifestations	Other features	Course	Relationship to streptococcal infection	Genetic factors	Serology	Imaging	Histology	Treatment options described
SC	Chorea	OCD & ADHD	Rheumatic fever	Monophasic (80%) Recurrent Persistent	Nearly all have evidence of preceding infection	D8/17 B cell marker	ASOT raised in 73% Anti-neuronal abs present in SC react with basal ganglia and GABHS	T2 hyperintensities of the CN, the GPI or the putamen and subcortical region of the white-matter Enlargement of BG	Encephalitis with inflammatory changes predominantly of the basal ganglia	Steroids, IVIG, PEX Penicillin prophylaxis
PANDAS	Tics	OCD, ADHD, anxiety, depression	None	Recurrent	31% culture positive	D8/17 B cell marker	ASOT raised in majority	Enlargement of BG	Unknown	PEX/IVIG Antibiotics when GABHS recurs
EL	Parkinsonism, dystonia, tics, blepharospasm, oculogyric crises	Sleep disturbance, anxiety, depression, mutism, catatonia, OCD	Encephalopathy, seizures, ophthalmoplegia, abnormal pupil responses	Monophasic (50%) Relapsing Static Progressive	URTI in over 50% 10% culture +ve	No data	ASOT raised in 65% Anti-BG Ab's in 95%	Normal in 60% Increased T2 signal in BG Brainstem/other areas occasionally involved	Perivascular lymphocytic cuffing, mainly in basal ganglia	PEX Steroids

Ab's antibodies, *ADHD* attention–deficit hyperactivity disorder, *ASOT* antistreptolysin-O titres, *BG* basal ganglia, *CN* caudate nucleus, *EL* Encephalitis lethargica, *GPi* globus pallidus pars interna, *IVIG* intravenous immunoglobulin, *OCD* obsessive–compulsive disorder, *PANDAS* pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, *PEX* plasmapheresis, *SC* Sydenham's chorea, *URTI* upper respiratory tract infection

Table 4 Summary of possible reasons for clinical variation between individuals suffering from a PI condition

Factor	System affected	Example
Host genetic differences	Immune system	SC and PANDAS(D8/17 B cell marker) [12, 15],
	Target organ (functional, immunological)	MBP polymorphisms may predispose to MS [41]
	Blood–brain barrier	Polymorphisms in the BBB regulatory protein CLDN4 affects susceptibility to EAE in rats [42]
Host environmental factors	Modification of immune response	HIV infection may predispose to ADEM [43]
	Decreased target organ reserves	Acute renal failure following streptococcal exposure more likely in congenital absence of one kidney [10]
	Characteristics of exposure to immunogenic pathogen (inoculum size, previous exposure)	Theoretical
	Modification of BBB	ADEM recurrence at previously affected site [29] or at site of surgery [30]. Localization of RE to areas of pre-existing brain pathology [44]
Pathogen	Epitope subtype	GlcNAc epitope in Streptococcus triggers development of SC [9]
	Factors affecting transportation	Theoretical
	Factors affecting toxicity	Theoretical

ADEM acute disseminated encephalomyelitis, *BBB* blood–brain barrier, *EAE* experimental allergic encephalomyelitis, *MBP* myelin basic protein, *MS* multiple sclerosis, *PANDAS* pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, *RE* Rasmussen's encephalitis, *SC* Sydenham's chorea

1. Lesion severity: a mild lesion leading to hyperkinesia may allow some degree of voluntary control of movements that would be defined as "tics", whereas a more severe lesion could preclude voluntary override and manifest as chorea.
2. Lesion localization: Clinical variability may reflect the disruption of different functional circuits located in diverse regions within the BG.
3. Varying levels of inherent pre-morbid "reserves" within the extrapyramidal system between individuals.

White-matter disorders

ADEM remains the prototype for the entire group of PI disorders. However, unlike grey-matter abnormalities, the nosological spectrum of PI white-matter conditions is poorly defined [24] and the role that an infection may play in triggering the onset and relapses in both MS [25] and neuromyelitis optica (NMO) [26] is still uncertain.

ADEM

ADEM is predominantly a disease of children and young adults and is often associated with antecedent infection or vaccination [27]. It tends to affect multiple brain and spinal-cord regions simultaneously and is usually monophasic, although both localized ADEM (as might be the case with transverse myelitis) [28] and recurrent ADEM [29] have been reported.

When ADEM recurs within the brain, there is a tendency for the same site to be affected [29]. The recurrence may reflect either a susceptibility of the physical barriers or antigenic modifications in certain brain regions as a result of an initial insult. This view is consistent with localized ADEM occurring in the region of an excised brain tumor [30] and with recurrent transverse myelitis taking place at the same segmental level [31].

Though ADEM is not a rare entity, basic information on its incidence, natural history, and optimal therapy is still lacking, especially regarding the adult population.

Consensus diagnostic criteria to facilitate the differentiation between ADEM and MS in children have recently been proposed [32]. These criteria recognize the high frequency of encephalopathy in children with ADEM, a feature which allows reliable discrimination from MS. Whether these criteria can reasonably be extrapolated to adults remains to be seen [32, 33]. This is primarily due to the higher incidence of ADEM as opposed to MS in children relative to adults, and the lower likelihood that an adult with ADEM will display features of an overt encephalopathy. The diagnostic guidelines proposed by the Brighton Collaboration Encephalitis Working Group [34] are intended for post-vaccination ADEM detection in both adults and children and thus cannot necessarily be applied to ADEM not associated with vaccinations. Establishing criteria that will enable a definite diagnosis of ADEM in adults [24] is important in order to: (1) facilitate recruitment of patients into prospective clinical studies, and (2) differentiate between ADEM and the first attack of multiple sclerosis (MS), since such a decision has therapeutic and prognostic implications. The therapeutic implications of differentiating MS from ADEM have encouraged investigators to search for ways to predict which patients

presenting with apparent ADEM will go on to develop MS [35]. A study that addressed this issue emphasized the presence of atypical MS symptoms (such as grey-matter involvement, alterations in consciousness) and the absence of CSF oligoclonal bands [35], but was criticized for lack of consideration of previously noted discriminating factors [36].

Clarifying the relationship between ADEM and MS will be a critical step in delineating the pathogenesis of these conditions. Can lessons learned from an animal model of ADEM, experimental allergic encephalomyelitis (EAE), be extrapolated to MS [37, 38]? Could "MS presenting as ADEM" actually be "MS *triggered* by ADEM"?

No controlled clinical trials for the treatment of ADEM have been completed, therefore recommendations are generally based on anecdotal data and expert opinion. A controlled clinical trial of plasma exchange in cases of acute severe attacks of inflammatory demyelinating disease in patients who have failed to improve after intravenous steroid therapy, sponsored by the NINDS, is underway and should not only guide clinical practice but may also shed light on some pertinent nosological discussions.

Vaccinations and ADEM

Vaccinations account for a small proportion of cases of ADEM, as most cases follow natural exposure to an infectious agent [39]. The propensity of a live pathogen to induce an immune response is expected to be greater than that of a vaccine, as viable microorganisms have a larger range of epitopes and also harbor the potential to induce cytotoxicity with a consequent cascade of events. There has been a marked drop in post-vaccination ADEM since the introduction of recombinant protein vaccines, which replaced vaccines cultured from CNS tissue [39, 40]. This supports the theory that some cases of post-vaccination ADEM were due to CNS tissue contamination of the original vaccines; a mechanism closely resembling EAE.

The future

While significant progress has been made in the area of PI CNS conditions, we have drawn attention to several issues that we feel are often neglected and require more intensive research. Addressing the following aims might enable a better understanding of the etiopathogenesis of these conditions and pave the way to rational and effective therapy.

1. Delineating the parameters distinguishing infectious from PI conditions. The possibility that many infections remain undetected or undetectable means that it is virtually impossible to exclude the possibility of a PI process in a wide range of neurological conditions, including neurodegenerative disorders.

2. Defining diagnostic criteria for the major PI conditions such as ADEM, SC and PANDAS.

3. Establishing a database to collect clinical information on individual PI cases that will facilitate the study of epidemiological and genetic factors influencing the occurrence of PI disorders.

4. Generating an animal model of PI BG dysfunction. This should further delineate pathogenetic, immunological, physiological and clinical parameters. Specifically, the possibility that all post-streptococcal BG diseases are different manifestations of the same condition should be investigated.

5. Designing multicenter treatment trials based on a uniform set of inclusion criteria and endpoints.

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