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SCIENTIFIC REVIEW

Therapeutic decision making in autoimmune and inflammatory disorders of the central nervous system in children

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ABSTRACT

Autoimmune and inflammatory disorders of the central nervous system can result in significant morbidity and mortality. Through the recognition of syndromes using diagnostic biomarkers, the clinician is now able to use immune suppressive therapies to improve outcomes. However, the therapeutic decision-making process is complex. The clinician has to balance the risk of disease, with the risk of treatment side effects. To achieve this balance, it is important to understand the natural history of disease, the risk of residual disability, the risk of relapse, and risk of a fatal outcome. It is also important to have some understanding of the pathological processes, as some of the entities have more reversible processes, whereas others have destructive processes. This review will assess the dynamic nature of this decision-making process, and compare some of the more severe diseases such as neuromyelitis optica, anti-N-methyl-D-aspartate receptor encephalitis and opsoclonus myoclonus ataxia syndrome, with disorders with more favourable outcomes such as Sydenham chorea and post-infectious cerebellar ataxia.

Keywords: autoimmune disorders; inflammatory disorders; multiple sclerosis; neuromyelitis optica; anti-N-methyl-D-aspartate receptor encephalitis; opsoclonus myoclonus ataxia syndrome; Sydenham chorea; post-infectious cerebellar

INTRODUCTION

Inflammation of the central nervous system is potentially life threatening and disabling. Through the discovery of biomarkers to define inflammation and diagnose specific diseases [1], clinicians are more willing to use immune suppressive agents to reduce inflammation in order to improve outcomes. However, immune suppressive therapies have side effects and it is therefore important to appreciate the risk of disability or death of the disease, and balance this with the risk of adverse events. This paper attempts to overview the clinical decision-making involved in this process, and is intended as a discussion document, rather than a guideline or systematic review.

OVERVIEW OF THE DISEASE SPECTRUM

Table 1 summarises the main inflammatory and autoimmune disorders of the central nervous system (CNS) that affect children. Multiple sclerosis is not discussed here, because it is dealt with in detail elsewhere, and the therapeutic pathways are different. The table does not constitute a systematic review of the literature, but instead samples the larger cohorts that report data on the severity of disease, risk of relapse and outcomes; nor is it exhaustive and does not consider rare or poorly defined disorders such as suspected autoimmune encephalopathy syndromes. The disorders are generally categorised into demyelination syndromes, autoimmune encephalitis, autoimmune movement and cerebellar syndromes, cerebral vasculitis and CNS complications of systemic autoimmune disease such as neuropsychiatric systemic lupus erythematosus (SLE).

UNDERSTANDING SEVERITY OF ACUTE DISEASE

In the past, CNS inflammation such as acute disseminated encephalomyelitis (ADEM) and Sydenham chorea was often observed and treated with symptomatic therapies only, as patients tended to improve. However it is now generally accepted that brain inflammation of any type is potentially damaging, and can result in permanent alteration of the CNS [14,15]. The severity of the acute disease is variable; ADEM and anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis often run a more severe acute course, often requiring intensive care (43 and 75% respectively) [2,6]. Being admitted to intensive care presents significant risk to the patient and is associated with poor outcomes [6], and trying to shorten the intensive care admission is important. By contrast, in many of these other conditions intensive care support is unusual.

Table 1. Understanding risk of relapse and risk of permanent disability (i.e. natural history)
We use large cohorts with adequately described data, children only. Cohorts are contemporary 'treated' cohorts, rather than 'natural history' cohorts. Unfortunately different publications use different definitions of 'favourable outcome'- in general this refers to normal outcome, but sometimes includes better outcomes with mild problems (modified Rankin score, mRS 0-2). The outcomes and deaths are those directly attributed to CNS disease, as opposed to other-organ disease effects (such as in SLE and Rheumatic fever).

Disease category	Disease	Relapse %	Favourable outcome %	Death	2nd line therapies used	Ref
Acute demyelinating syndromes	Acute disseminated encephalomyelitis (n=84)	10%	89% ^	<2%	No	[2]
	Transverse myelitis (n=95)	17%	70%##	<2%	Occasional	[3]
	Optic neuritis (n=36)	36%	80%	<1%	No	[4]
	Neuromyelitis optica (n=20)	90%	<50% **	<5%	Yes	[5]
Autoimmune encephalitis	Anti-NMDAR encephalitis (n=211 children)	12%	58%	3%	Yes	* [6]
Autoimmune movement and cerebellar syndromes	Opsoclonus myoclonus ataxia syndrome (n=105)	52%	25%	<2%	Yes	[7]
	Sydenham chorea (n=24)	42%	90%^^	<1%	No	[8]
	Cerebellitis (n=11)	<10%	<50%	~5-10%	No #	[9]
	Post-infectious cerebellar ataxia (n=73)	<5%	89%	<1%	No	[10]
Cerebral vasculitis	Primary angiitis of CNS (n=19)	42%	70%	<5%	Yes	[11]
CNS complications of systemic autoimmune disease	Neuropsychiatric SLE (n=100)	20%	75%	3%	Yes	[12]

* Child only data, apart from relapse rate (child and adult)
** at follow-up after relapsing course. Monophasic disease can have significantly better outcomes.
^ Expanded disability status score, EDSS 0-2
^^ Persistent mild chorea, and persistent psychiatric symptoms are common, although severe problems are uncommon
# Cerebellitis is a severe syndrome with potential risk of death (due to herniation) and disability, however the disease is rare and poorly understood, and so 2nd line therapy is not promoted (although could be justified)
The largest cohort of transverse myelitis reported better outcomes than previous cohorts which reported <50% favourable outcomes [13].

UNDERSTANDING RISK OF PERMANENT DISABILITY

A further important consideration is the risk of permanent disability. This risk is partly related to the initial episode, but also related to the accumulative damage associated with disease relapses. For example, relapses increase disability in neuromyelitis optica (NMO), although patients can be left with permanent disability after a single event, partly related to the severity of the pathology (discussed later). As presented in Table 1, the risk of permanent disability varies by disease. However, the information provided in Table 1 does not adequately address the complexity of this issue. For example, in Sydenham chorea, historically considered a 'benign' disorder requiring no treatment, a significant proportion of patients are left with permanent neuropsychiatric alteration or residual mild chorea - not enough to represent 'major disability', but potentially life altering [15,16]. Likewise, the residual cognitive deficits after ADEM are probably under-reported and under-appreciated [17-19]. However, for some of these disorders, such as NMO, anti-NMDAR encephalitis and cerebral vasculitis, the risk of permanent disability is significant, and therefore it is easier to rationalize more potent immune suppression to try to improve outcomes [6].

There is now reasonable retrospective evidence in NMO, anti-NMDAR encephalitis, opsoclonus myoclonus ataxia syndrome (OMAS) and cerebral vasculitis, that more potent immune suppression and use of second line therapies (as discussed later) improve the course of the acute disease, reduce relapse and improve long-term outcomes [6,11,20,21]. However, there are no randomized controlled trials in these rare disorders to provide a strong evidence for this approach at this time.

UNDERSTANDING SPEED OF RECOVERY AND PERSISTENT CNS INFLAMMATION

The ability to determine when a patient is not following the expected speed of improvement is very challenging, and often requires previous experience with these conditions. The different disorders require different expectations, which will influence therapeutic decision-making. For example in acute ADEM and transverse myelitis, there is typically a rapid improvement during the first days after starting intravenous methylprednisolone, and poor improvement after 5-7 days may alert the clinician that the patient is not following the expected trajectory, and escalation of therapy should be

considered. By contrast, patients with anti-NMDAR encephalitis (particularly when the disease is diagnosed later) will not respond rapidly to immune suppression, and it is recommended to wait 10-14 days after first line therapy before escalating [6]. However this decision is further complicated by the severity of disease. For example, a patient with anti-NMDAR encephalitis who has the 'full syndrome' with respiratory and autonomic dysfunction on intensive care is at high risk, and so escalation to second line therapy should be considered early, whereas milder patients on the ward may be observed for a longer. However, there is a general theme emerging for autoimmune CNS disorders, that early immune therapy improves outcomes and thus should not be delayed, particularly in very symptomatic or critically ill patients [21]. Furthermore, patients with anti-NMDAR encephalitis often take a long time to recover, require prolonged hospital admissions, and improvements continue for up to 2 years [6]. Defining when a patient is not improving adequately is challenging, and the autoantibody biomarkers should generally not be used in this decision making process, as antibodies can remain positive in serum and cerebrospinal fluid (CSF) for years, and titres are not very reliable in monitoring of disease (although tend to reduce with improvements, and increase with relapses). Instead, other markers of CNS inflammation are probably more useful such as CSF neopterin [22], although there is a paucity of CSF and brain inflammatory biomarkers available in clinical practice, and there are few biomarkers that have been used longitudinally to determine disease progress. A recent study showed that the chemokine CXCL13 is elevated in CSF in anti-NMDAR encephalitis, and is more elevated in patients who have a poor outcome or relapse [23]. Biomarkers that can help in disease monitoring, in addition to clinical monitoring are required, as determining when a patient is failing to improve is a major management challenge to clinicians.

UNDERSTANDING RISK OF RELAPSE

A crucial factor in deciding longer term maintenance immunotherapy is the inherent risk of relapse. Aquaporin-4 (AQP4) antibody positive NMO is typically relapsing (table 1) [5]. It is accepted that relapse prevention reduces disability in NMO, and therefore reducing relapses should be a primary consideration, and it would be appropriate to plan maintenance immune suppressant regimen even at the first acute event. By contrast, many of the other conditions are predominantly monophasic (Table 1), where longer term immunotherapy is often considered only at relapse. It should be noted that the risk of relapse in many of these disorders has changed compared to earlier descriptions. For example, for anti-NMDAR encephalitis, the relapse rate was ~25% initially, but with increasing immune suppression in the acute phase, the relapse rate has reduced to ~12% [6]. A similar phenomenon has occurred in OMAS [20,24]. There is emerging evidence that the relapse risk is influenced by early and perhaps more systematic immune suppression in the acute presentation [6,25].

UNDERSTANDING NEUROPATHOLOGY AND REVERSIBILITY OF DISEASE

Table 2 attempts to summarise the pathological processes occurring in these disorders, which are variable. It is important to appreciate this variability, as these disorders are not the same, for example it is reasonable to undertake 'watchful waiting' in Sydenham chorea or post-infectious cerebellar ataxia, whereas in more severe indications such as NMO and cerebral vasculitis, it is reasonable to escalate quickly to second line therapies (or even use second line therapies at initiation of therapy).

The pathology of many CNS autoimmune and inflammatory disorders is often inferred from limited cases that are often poorly clinically defined, or are biased towards atypical or severe cases (such as post mortem cases). Additionally cases studied usually reflect chronic rather that acute pathobiology. In many of the disorders, a perivascular lymphocytic infiltration is common, and not very specific for any particular entity. A study of autoimmune encephalitis pathology in adults noted significant variability in pathology [34]. For example in anti-NMDAR encephalitis, there is a lymphocytic infiltration predominantly of plasma cells, and in vitro [32] and animal studies [33] consistently demonstrate that the effect of antibody on neurons and disease symptomatology is reversible, as is often observed in patients, although this may take up to 2 years [6]. By contrast, NMO is a destructive pathology, with cavitation and astrocyte loss, complement mediated cytotoxicity, and secondary demyelination [27]. NMO pathology involves T-lymphocytes, neutrophils, eosinophils, as well as autoantibody-mediated pathology [27]. Therefore more potent immune therapy is justified to prevent irreversible astrocyte loss and its downstream effects on neuropathology. Likewise, cerebral vasculitis often has associated cell death with secondary hypoxic ischaemic brain injury, which is irreversible [32]. Neuropsychiatric SLE is complex with many clinical syndromes, and multiple complex pathophysiological processes (immunological, vascular, or both), and may require immune suppressive and anti-thrombotic therapies [35]. It is important to understand the pathological process of the disease we are treating, as more potent immune suppression can be justified, when more destructive and irreversible pathobiology has been established.

UNDERSTANDING INTRATHECAL AUTOIMMUNITY AND THE ROLE OF THE BLOOD BRAIN BARRIER

A key conundrum in these disorders is if the inflammatory process is 'established' in the CNS or is driven systemically. In anti-NMDAR encephalitis, there is clear evidence of an active intrathecal inflammation with CSF pleocytosis, intrathecal oligoclonal bands, and intrathecal production of NMDAR antibodies. By contrast, in other disorders, such as ADEM associated with anti-MOG antibodies, there is typically not intrathecal production of autoantibody, although the timing of testing is likely to influence some of these findings [36].

Knowing if neuroinflammation is predominantly driven centrally or peripherally may influence how we choose or direct therapy. Plasma exchange (PLEX) will remove circulating antibody, lymphocytes and other molecules, and will subsequently result in less circulating immune molecules entering the CNS, but PLEX will not necessarily reduce established intrathecal inflammation (when present), so it should probably not be used in isolation in anti-NMDAR encephalitis, but instead should be used in conjunction with corticosteroids or other agents that have access to the CNS.

A further poorly investigated consideration is the role of the blood brain barrier (BBB) in these disorders. It is often assumed and cited that the BBB is altered or disrupted in inflammatory CNS syndromes (although not necessarily proven), extrapolated from studies in multiple sclerosis.

Table 2. Pathological findings in the autoimmune and inflammatory CNS disorders. The symbol (-) denotes there is inadequate literature.

Disease category	Disease	Summary of brain pathology	Ref
Inflammatory demyelination	Acute disseminated encephalomyelitis	Perivenular lymphocytic infiltration (predominantly T cells) with only minor demyelination.	[26]
	Transverse myelitis	-	
	Optic neuritis	-	
	Neuromyelitis optica (AQP4 ab)	Astrocytopathy with secondary demyelination. Perivascular inflammation with adaptive (B and T cells), and innate (neutrophils, eosinophil) activation. Immunoglobulin and complement deposition. Destructive and cavitating pathology.	[27]
Autoimmune encephalitis	Anti-NMDAR encephalitis	Perivascular lymphocytic infiltration (predominant plasma cell), absence of complement.	[28]
Autoimmune movement and cerebellar syndromes	Opsoclonus myoclonus ataxia syndrome	Sometimes little pathological abnormalities. Periaqueductal inflammatory cells.	[29]
	Sydenham chorea	Perivenular inflammation, predominantly involving striatum.	[30]
	Cerebellitis	Cerebellar leptomeningeal and parenchymal lymphocyte (T and B) and eosinophil infiltration.	[31]
	Post-infectious cerebellar ataxia	-	
Cerebral vasculitis	Primary angiitis of CNS	Inflammatory infiltrate (predominantly lymphocytes) located in intramural blood vessels. Secondary ischaemia.	[32]
CNS complications of systemic autoimmune disease	Neuropsychiatric SLE	Variable with either dominant thromboembolic, ischaemic or haemorrhagic features.	[33]

Whilst reducing BBB disruption, such as treating infection and trying to reduce the BBB permeability can be, in theory, of value [37], this strategy may significantly reduce the CSF penetration of immune therapy.

THERAPIES AND MECHANISMS

Acute therapy

Figure 1 demonstrates the generally accepted pathway for treating inflammatory and autoimmune CNS disorders.

First line acute therapies are often corticosteroids, intravenous immunoglobulin (IVIG) and PLEX, used sequentially or in combination. Despite the paucity of good reported evidence of efficacy, IVIG is often used by many paediatric neurology centres and is generally considered to be useful. However, it is expensive and availability may often be restricted. PLEX is technically difficult, and is less accessible as a result of this, particularly in the very young child. There is a paucity of literature regarding the safety and tolerability of PLEX in young children with autoimmune CNS disease.

In most clinical situations steroids are initiated first followed by IVIG, and following that PLEX. IVIG may be used first instead of steroids if there remains some uncertainty of acute invasive infections. In situations, such as a child with severe CNS inflammatory disorder like anti-NMDAR encephalitis requiring intensive care support, where PLEX is considered likely to be necessary, it would be pragmatic that IVIG be considered post PLEX, avoiding the inadvertent removal of IVIG by PLEX and therefore ameliorating its effect. The mechanisms of action, the speed of action, and the side effects of the first and second line therapies are presented in brief in table 3.

When CNS inflammation is refractory to 1st line therapy, second line therapy can be considered such as rituximab and cyclophosphamide (separately or together), but these should be reserved for diseases with higher risk such as anti-NMDAR encephalitis, NMO, OMAS, cerebral vasculitis and neuropsychiatric SLE [21]. Steroid sparing agents such as azathioprine and mycophenolate mofetil (MMF) take 3-6 months to be effective so are not useful if a more immediate effect is required. On occasions neurosurgical intervention is required in the treatment of malignant brain oedema as seen in cerebellitis and less commonly in ADEM [9].

Maintenance therapy

Once the acute therapy is complete, if there is a risk of relapse that is considered significant (as discussed above), then chronic immune suppression can be considered. Azathioprine and MMF are most commonly used in this setting, but due to the latency of their effect, steroid cover (or other immune therapy) will be needed until the drugs are effective. An alternative approach is monthly IVIG but this is expensive and may be less effective in some disorders such as OMAS [20]. An alternative approach to chronic immune suppression is re-dosing rituximab. Rituximab usually produces 6 months of demonstrable B cell depletion, although can last >12 months in 10% of treated patients [21]. In disorders when the risk of relapse is high (in frequency and severity), such as NMO, re-dosing of rituximab can be considered. If re-dosing of rituximab is planned, it is important to appreciate the

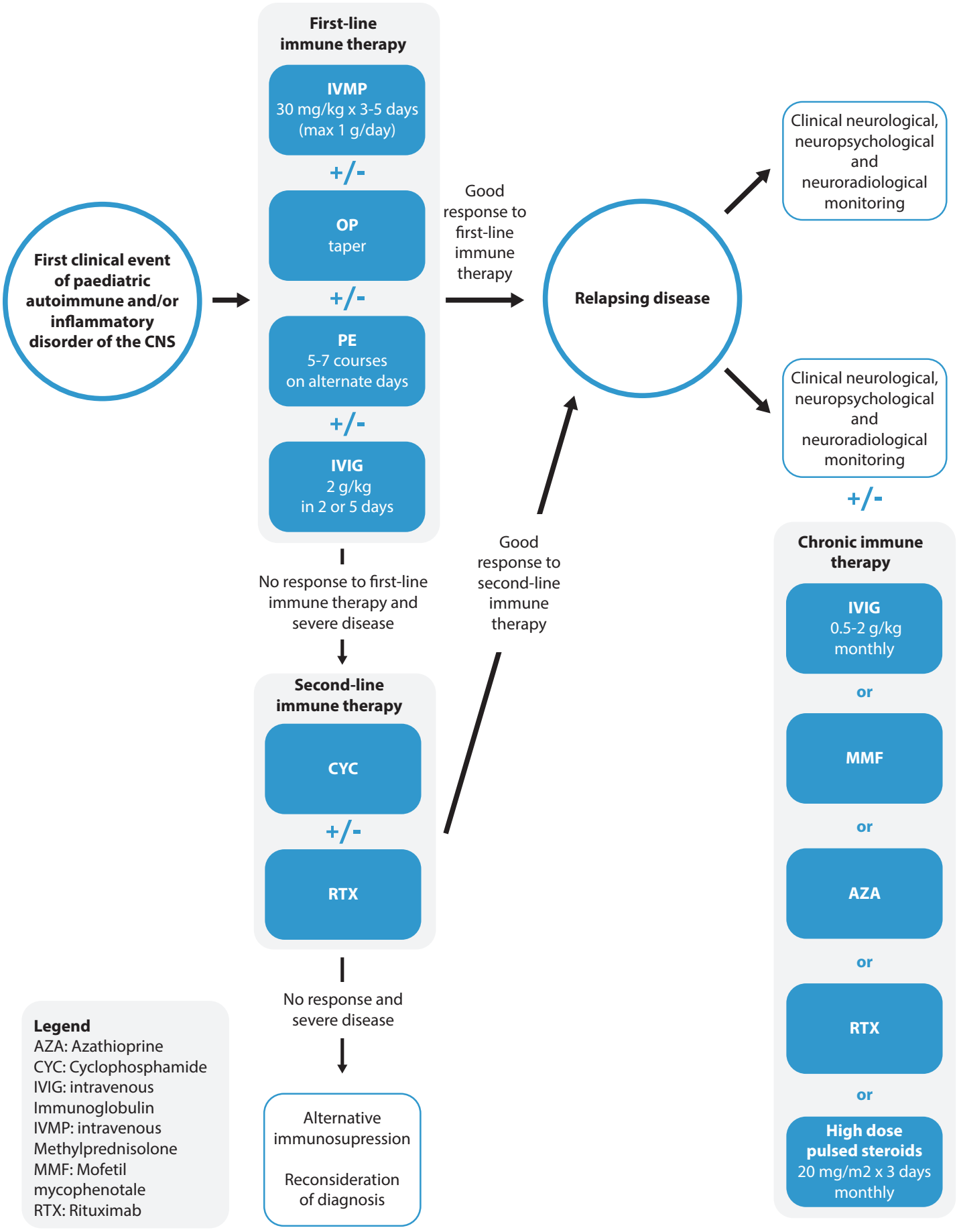

Figure 1. Trial of first line therapy in confirmed or suspected autoimmune CNS disease. If the patient fails to respond to first line therapy, and the disease has significant risk of morbidity or mortality, then second line therapies can be considered. If the disease has a relapsing course, or has a high risk of relapse, chronic immune suppression can be considered.

Table 3. First and second line drugs used in the treatment of autoimmune and inflammatory CNS disorders-mechanism of action, speed of action and common or concerning side effects

Drug	Mechanism of action	Expected time for drug effectiveness	Concerning side effects
1ST LINE IMMUNOTHERAPEUTIC AGENTS			
Corticosteroid	Broad anti-inflammatory properties, reduce swelling and oedema, reduce permeability of BBB.	Hours/days	Lots of transient side effects: hypertension, glycosuria, CNS effects, catabolic effects. Long term effects: Bone mineralisation, skin thinning, infection, cataract, growth suppression, cushingoid habitus, metabolic problems.
Intravenous immunoglobulin	Multiple immune mechanisms involving antibody, cytokines, cellular.	Hours/days	Expensive, allergy, risk of viral transmission.
Plasma exchange	Plasma filtration, remove antibody and cytokines.	Hours	Invasive, haemodynamic alteration, large vessel access required, infection.
2ND LINE OR MAINTENANCE IMMUNOTHERAPEUTIC AGENTS			
Steroid sparer (azathioprine, mycophenolate mofetil)	Broad cellular immune suppressant.	~3 months	Liver dysfunction, increased risk of infection, increased cancer risk (small), expensive (MMF).
Rituximab	B cell depleter, secondary effects on T cells.	1-4 weeks	Infusion side effects common but not serious, ~1:40 chance of severe serious infection, expensive.
Cyclophosphamide	Broad cellular immune suppressant.	Days	Cystitis, renal toxicity, infection, cancer, infertility.

BBB: blood-brain barrier

timing of B cell repopulation using frequent B cell monitoring to prevent the patient relapsing during B cell repopulation [38]. Alternatively rituximab can be re-dosed regularly (for example every 6 months) although this may in theory result in increased side effects [43].

UNDERSTANDING RISK OF TREATMENT

It is very important to consider the risk of treatment, as outlined in brief in table 3. The majority of these treatment side effects are clearly outlined in respective national therapeutic formularies, such as the British National Formulary in Children (BNFC), where the majority of data is assimilated/derived from the summary of product characteristics (SmPC). However, children may be resistant to some of these side effects, but vulnerable to others [39]. Furthermore, predicting more severe adverse effects remains challenging, as is the knowledge of the precise incidence of adverse events. Polymorphisms of the thiopurine S-methyltransferase (TPMT) gene that determine the metabolism of thiopurines such as azathioprine has an established role in screening for patients at risk of adverse effects [40]. However, application of this for other immune therapeutic agents remains unestablished, nor is the role of such pharmacogenetic stratification in optimizing treatment [41]. Sick children on intensive care are at risk of infection, and immune suppression with multiple agents presents significant potential risk [21]. For example, a serious infectious side effect that was attributed to immune suppression was described in 4 of 144 children receiving rituximab for severe inflammatory CNS disorders [21]. Likewise, cyclophosphamide brings concerns about malignancy and infertility, as well as infection, although most safety data is derived from adult trials [42]. And azathioprine and MMF brings risks of infection and a slight increase in risk of malignancy. These side effects should be considered during the decision-making process, and for this reason, these more potent immune suppressants should be reserved for more significant diseases that carry inherent risk of disability or death. Some of these therapies are not available in resource-poor countries. However, many of these conditions are responsive to steroids, and can be used in regimens to attempt to minimize accumulative side effects (such as monthly pulse regimens). Clinicians should use the corticosteroid they are most familiar with- there is little data to suggest any particular corticosteroid is superior in this context.

COUNSELING AND INFORMING THE FAMILIES

Families and patients need to be informed about the relative risks of therapy, but this needs to be presented in a way that helps the family understand that the risks of not giving the drug may result in permanent neurological disability. Often this is conducted with extrapolated data and is hugely influenced by clinician familiarity with specific agents and/or experience of adverse events. This counseling is complex, and unfortunately can result in families and clinicians becoming ‘risk averse’ or ‘therapeutically incapacitated’. A confident but honest approach is probably most likely to succeed.

SUMMARY

Figure 2 illustrates the complex decision-making process, trying to weigh up the risk of the disease with the risk of the therapy. We are currently in a transitional phase in our understanding of these newer disorders. Biomarkers have recently informed us about diseases that are treatable. We are starting to understand that immune suppressive therapies improve outcomes, reduce relapses and reduce disability. However, the therapies are currently hugely empirical and based on a generic rather than a disease specific strategy. Furthermore, we lack directed therapies that could be more effective and better tolerated. There is a significant shortage of randomized controlled trials in these disorders, and the evidence base is only provided by retrospective cohort data and personal opinion that may be biased by experience. Collaborative international endeavors are imperative to provide progress.

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Competing interests

None

Author contributions

First draft by RCD, subsequent discussions, editing and re-writing by all authors.

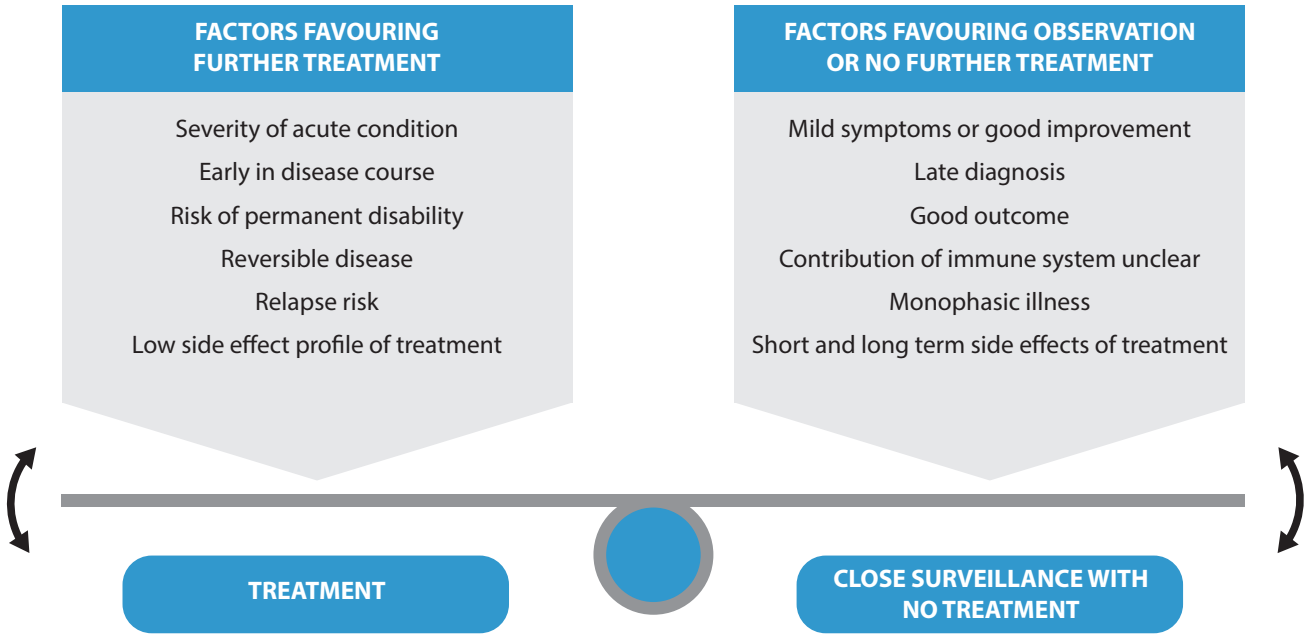

Figure 2. The complexity of therapeutic decision-making: Balancing the risk of disease with risk of drug side effects. The figure demonstrates some of the variables involved in therapeutic decision-making.

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