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IMMUNOTHERAPY FOR ARTERIAL ISCHAEMIC STROKE IN CHILDHOOD: A SYSTEMATIC REVIEW

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ABSTRACT

Background: There is little evidence about either prevention or treatment of childhood arterial ischaemic stroke (AIS). However drugs that regulate the immune and inflammatory response could theoretically prevent occurrence or recurrence of AIS. Additionally, as an acute treatment they may limit the neurological damage caused by AIS. Here we systematically review the evidence on the use of immunotherapy in childhood AIS.

Design: A systematic review of publications in databases Embase and Medline from inception. All types of evidence were included from trials, cohorts, case-control and cross-sectional studies, and case reports.

Results: Thirty-four reports were included: 32 observational studies and two trials. Immunotherapy was used in two key patient groups: arteriopathy and acute infection. The majority were cases of varicella and primary angiitis of the CNS. All three cohorts and 80% of the case studies were treated with steroids. Recurrence rates were low. Analytic studies weakly associated steroids with lower odds of new stroke and neurological deficits, and better cognitive outcomes in the context of Moyamoya disease and tuberculosis.

Conclusions: Immunotherapies are used in children with AIS, mainly as steroids for children with arteriopathy. However there is currently little robust evidence to either encourage or discourage this practice. There is weak evidence consistent with the hypothesis that in certain children at-risk, steroids may both reduce the risk of occurrent/recurrent stroke, and enhance neurological outcomes. As the potential benefit is still uncertain, this indicates that a trial of steroids in childhood AIS may be justified.

BACKGROUND
Childhood Arterial Ischaemic Stroke (AIS) affects 1.6 per 100,000 children per year in the UK.[1] Case fatality is estimated as 9-15%[2-4] and many survivors have neurological or functional impairments.[4-6] Estimates of recurrence vary from 1-37%, with the highest rates consistently found in children with vascular pathologies.[4 7 8] Currently there is little evidence on how to prevent childhood AIS, or how to best to treat it.

Immunotherapy can be defined as the prevention or treatment of disease via substances that modulate the body's immune and inflammatory responses.[9] Theoretically immunotherapy has a potential for two roles in AIS: firstly to prevent either primary or recurrent AIS, and secondly as a potential treatment of AIS which may improve neurological outcomes.

**Prevention:**

Many cases of childhood AIS have an immunological/inflammatory aetiology that causes an arteriopathy. E.g. primary or latent-reactivated varicella zoster virus (VZV) can lead to infection and inflammation of the cerebral arteries, thereby increasing the risk of AIS.[10]

Other infections such as enterovirus[11], mycoplasma pneumonia[12-14] and herpes virus[15] have also been implicated in arteriopathy-related childhood stroke. Recent studies[1 16] have found arteriopathy in over a third of cases, and earlier studies have had even higher estimates.[7 17-20] In cases of arteriopathy, immunotherapy may ameliorate the disease process by reducing arterial inflammation. In theory this should reduce the occurrence or recurrence of AIS.

**Treatment:**

The acute and adaptive inflammatory immune response to ischaemic insult contributes to brain tissue damage[21 22] and it was recently demonstrated in a small pilot study that
inflammatory markers were elevated in children with AIS compared to controls.[23] This implies that pharmacological control of the immune response could help limit this damage, and thereby improve outcomes. In animal models, immunotherapy has been associated with smaller total infarct size and improved cognitive and functional outcomes.[24-29] In humans, steroid trials in the 1970s-80s in adults found little or no evidence of efficacy, and treatment was sometimes associated with worse outcome.[30-32] One was a small trial[32] (n=53) which found that patients given dexamethasone within 24 hours of cerebral infarction had slightly worse outcomes than those given placebo, with lower improvement in neurological deficit at 29 days, slightly higher mortality and higher rate of treatment complications (mainly infections). However a larger trial[31] (n=113) carried out a decade later by the same group found no significant difference in outcome and in fact the dexamethasone group in this trial had fractionally lower mortality. A still larger but retrospective study[30] (n=556) compared patients given dexamethasone to those given only anti-platelet therapy and glucose. Patients receiving dexamethasone had slightly worse outcomes than those who did not, but this result is confounded by severity as it was patients who were worse off at baseline who were treated with steroids.

More recently minocycline, a tetracycline antibiotic that modulates the immune response via inhibition of T cell migration and microglial activation, has been investigated in adult AIS and was associated with improved neurological outcomes.[33] However, inference from adult trials is not straightforward as the aetiology of stroke in adults is significantly different to children, in whom the predominant risk factors related to lifestyle and old age[34] do not apply. If steroids were effective in the population of strokes with an immunological/inflammatory aetiology, as is more common in children, this is unlikely to have been picked up in adult trials. Although immunotherapies have not been formally trialled in childhood AIS specifically, they have been demonstrated to be a safe and effective
treatment in children in other inflammatory conditions of the CNS, such as vasculitis and lupus.[35-38]

These considerations suggest that immunotherapy could have two potential roles in AIS: firstly to prevent either primary or recurrent AIS, and secondly as an acute treatment which may improve neurological outcomes. In line with these theoretical considerations, a recent survey has shown that there is consensus among experts in the field that the most important trial to be done in childhood stroke is an RCT of steroids in AIS.[39]

One complication in considering treatment is that after the active immune response in the acute phase of AIS, there follows a generalised immunodepression which leaves patients susceptible to infection, significantly increasing morbidity and mortality from stroke in adults.[40 41] This has not yet been studied in children, but clearly risk of infection would have to be monitored carefully in the context of steroid treatment. A recent systematic review of toxicity of short-course oral corticosteroids in children (in a range of diseases) found that the rate of major secondary effects was low.[42] The most common adverse effects were vomiting, changes in behaviour, and sleep disturbances, with an incidence around or below 5% of cases. The most serious side effect of treatment was infection, although this occurred in less than 1% of cases.

The current standard treatment in adult acute AIS is thrombolysis. A trial of thrombolysis in paediatric stroke, the TIPS trial, has recently been attempted (2012) but was closed early due to challenges in recruiting sufficient numbers.[43] One of the key issues is that thrombolysis needs to be given in the first 4-5 hours after onset of AIS. Although there is excellent recognition of adult stroke enabling prompt treatment, paediatric stoke is often not diagnosed until well after this treatment window has passed. A recent study in the UK demonstrated that
the median time from symptom onset to diagnosis in childhood AIS was 24 hours (IQR 7-76 hours).[44]

METHODS

We carried out a systematic review of the evidence for the use of immunotherapy in childhood AIS. Aims were to elucidate how immunotherapies are being used, and review evidence on whether immunotherapy is associated with reduced risk of recurrence, and improved neurological outcomes.

Inclusion/Exclusion criteria:

Types of study included were randomised and non-randomised trials, cohort, case-control and cross-sectional studies, case series and case reports. The rationale for such broad inclusion criteria is that evidence on this topic was expected to be scarce.

Populations included were children age 30 days to 18 years with AIS confirmed by neuroimaging. Children with Haemorrhagic Stroke or Cerebral Venous Sinus Thrombosis were excluded as neither of these have a theoretical basis for response to immunotherapy. Children with sickle-cell disease were excluded as they comprise a well-delineated sub-population, in whom much more is known about stroke treatment and prevention. Stroke in the context of systemic arteritides such as juvenile systemic lupus erythematosus or Takayasu Arteritis was excluded, as these children are likely to be on steroid therapy for their prior disease rather than specifically as treatment for stroke.
Treatments included were any immunosuppressant (steroid-based or steroid-sparing) given in any format, dose and regimen, and whether as a sole or combination therapy. Again the rationale is that there was unlikely to be sufficient data on any one type of therapy alone.

Primary outcomes of interest were incidence of recurrent AIS, and general neurological recovery (motor, functional, cognitive, behavioural and affective outcomes). Secondary outcomes were death, other cerebrovascular events, and other adverse events related to treatment. Follow-up periods of any duration were included.

For the purposes of summarising data, outcomes were categorised as: complete recovery; mild residual deficits; moderate residual deficits (enough to require daily support); severe residual deficits (e.g. quadriplegia, severe cognitive impairment). Categorisation of outcome was made on the basis of the description given by the original report authors.

Search and data collection:
Search strategies were constructed and run on the electronic databases Embase and Medline. Search terms were concepts/synonyms for AIS and immunotherapy. A complete search strategy is available from the authors. There were no date restrictions.

Search results were exported into the electronic referencing system Endnote X7. Titles and abstracts were screened and then full text reviewed for all potentially relevant results. References of included studies and reviews were screened for identification of further potentially eligible results.
A standardised electronic data collection form was used to abstract data. This included study type, demographic and clinical data, treatment data, follow-up and outcomes.

*Analysis:*

Planned analyses were, as far as data allowed, to examine for the association between immunotherapeutic treatment and each outcome of interest. If results allowed we intended sub-group analyses by aetiology (suspected infectious/inflammatory, or not), type of immunotherapy, dose, duration of therapy, lead time to treatment, and age group.

**RESULTS**

From 432 initial search results and 83 potential extras from reference lists, 34 reports were included (Figure 1). Clarification was sought from authors for reports that potentially included overlapping cases,[45-47] and all necessary clarifications were provided.

Of the included results (see online supplement) there were 18 case reports, 10 case series, four cohort studies and two RCTs. In some reports only a sub-section of patients were relevant. The date range of publications was 1984-2013. Twenty-nine reports gave individual-level data and five reports gave group-level data only. The individual-level data collectively described 37 children (mean age 8.9 years (sd 4.8), 21/37 (57%) female). The group-level data collectively described 115 relevant patients.

*Individual data:*

Immunotherapies were used in two main patient groups: vasculitis/arteriopathy; and acute infections (Figure 2). The most frequent suspected causes were VZV (13/37, 35%) and
childhood Primary Angiitis of the CNS (cPACNS, also called CNS Vasculitis and Isolated Angiitis of the CNS) (12/37, 32%). Eight of the 12 cPACNS cases (66%) affected the large-medium vessels. When combining all cases of arteriopathy together, 30/34 (88%) affected the large/medium vessels.

Eleven types of immunotherapy were reported, and more than one immunotherapy was used in 16/37 cases (43%). The mean number of immunotherapies used was 1.8. When considering all uses of immunotherapies together, 80% were steroids, most commonly prednisone and methylprednisolone (Figure 3).

In 13/37 cases (35%) treatment was solely with immunotherapy. In the other cases acyclovir (12/37, 32%), aspirin (9/37, 24%), and antibiotics (4/37, 11%) were the most commonly reported conjunctive therapies. Antimalarials, antiepileptics, verapamil, Heparin and unspecified antithrombotics were reported in ≤3 cases each. In total 15/37 (41%) were reportedly treated with some form of antithrombotic (combining those on aspirin, heparin, LMWH, and unspecified antithrombotics). It is possible that these and other conjunctive therapies were used more frequently, but not reported by the study authors.

Median follow-up time was 12 months (range 3 days to 9 years) although in four cases duration of follow-up was not reported. There was only one recurrent stroke (3%) in a case of stroke after a severe episode of VZV and vasculitis[48], and two deaths (5%). One death was in a case of stroke after persistent VZV infection in the context of AIDS, where the child secondarily developed pneumonia[49]. The other death was in the case of a young girl with isolated angiitis of the CNS and stroke who had recently started the contraceptive pill[50]. 17/37 (46%) were described as complete recoveries/asymptomatic at last follow up, 10/37
(27%) with mild residual deficits, 5/37 (14%) with moderate, and 2/37 (5%) with severe residual deficits. In 1/37 the outcome was not sufficiently reported (Figure 4). Sub-group analysis was not appropriate due to the small number of cases, but a breakdown of further data on individual cases is given in Appendix A.

*Group data:*

One cohort was 68 medium-to-large vessel cPACNS cases, including 50 with previous AIS,[51] mean age 8.5 years (sd 3.5). As arteriopathies, all of these cases would be at-risk of AIS occurrence/recurrence. All were treated with immunotherapy: IV prednisone and immunoglobulin acutely, followed by oral prednisone and azathioprine for cases the authors categorised as ‘progressive, obliterative’ arteriopathies based on neuroimaging. Follow-up was 24 months. There were no recurrent strokes. 2/50 died (4%). General neurological outcomes were: 20% complete recovery, 25% minor disabilities, 20% moderate, and 35% severe disabilities. Sub-group analysis of neurological outcomes was not given for those with and without previous AIS.

Another cohort was 45 cPACNS cases,[45] median age 9.8 years (range 3.3-17.8). 19/45 had angiography-positive disease (affecting the large/medium vessels) and 26/45 had angiography-negative disease (affecting the small vessels). Treatment was as per institutional protocol. For angiography-positive disease, the treatment protocol appeared to be heparin plus antiplatelet therapy. It is stated that more recently corticosteroids was added to the protocol for this group but it is unclear how many received steroid therapy. For angiography-negative disease, the treatment protocol appeared to be induction with IV cyclophosphamide and prednisone, followed by maintenance therapy with either azathioprine or mycophenolate.
mofetil. The exact number receiving azathioprine or mycophenolate mofetil or both was not clear. Within the whole cohort, 19 cases had evidence of previous probable AIS, 2 of which had angiography-negative disease. Median follow-up for the whole cohort was 21.6 months (range 3-36 months). There were no reported deaths nor any new or recurrent strokes in any of the children in this cPACNS cohort, either in the angiography negative disease group (all of whom will have been receiving immunotherapy) or the angiography positive group (an undetermined number of whom will have received immunotherapy in the form of steroids in addition to heparin and an anti-platelet agent). For the overall cohort, the median Pediatric Stroke Outcome Measure (PSOM) score improved from 2.25 at the time of diagnosis to 0.5 at 12 months, and 0 at 24 months (zero indicating no neurological deficits). The PSOM scores were unfortunately not broken down by treatment group or by history of previous AIS.

A cohort of 166 children with bacterial meningitis included 14 presenting with AIS, and 6/14 treated with immunotherapy (dexamethasone) in addition to antibiotics.[52] The mean age was 1.3 years (range 3-36 months). Follow-up was for a minimum of 12 months. There were no recurrent strokes. 3/14 (21%) died and 8/14 (57%, including all 6 on immunotherapy) were reported as ‘poor outcome’ (including blindness, hydrocephalus, institutionalisation, quadriplegia, severe mental retardation and uncontrolled seizures). Outcomes were not consistently separated for those on treatment. Authors felt there was no evidence of the effectiveness of dexamethasone, although as it was only given to the most severe/clinically deteriorating cases, these results are confounded by severity.

There were two RCTs that while not directly trialling immunotherapy in AIS, did contain relevant results. One compared anti-tuberculosis treatment plus prednisone, to anti-tuberculosis treatment alone in 138 children with Tuberculous Meningitis.[53] 16/68 (24%)
in the steroid group and 17/70 (24%) in the non-steroid group presented with AIS. At 6 months the steroid-treatment group had lower incidence of new stroke (OR 0.67) although this was not statistically significant (p=0.14). They also had significantly greater improvement in cognitive function (OR 2.19, p=0.038 for IQ>75); and lower mortality (OR 0.32, p=0.015) compared to controls. Outcome data applied to the whole group so it is not clear if the effects are the same in the sub-group with previous stroke.

Another trial compared general anaesthesia (GA) plus nerve block (methylprednisolone+bupivacaine) to GA only, in 39 children (mean age 8 years, range 3-13) undergoing surgery for Moyamoya disease.[54] Within 24 hours of surgery there was higher incidence of new stroke, and neurological deficits in the control group compared to those treated with methylprednisolone+bupivacaine (OR 3.2, 95% CI 0.6 to 18.4). The study was underpowered to detect a statistically significant difference in outcome, but results are suggestive of a protective effect of treatment. The report’s authors speculate that the lower incidence of stroke in the treatment group may be related to better pain control and/or more stable cerebral blood flow, but it may also be related to the immunomodulating and anti-inflammatory effect of methylprednisolone.

**DISCUSSION**

This review was a systematic evaluation of the evidence on the use of immunotherapy in childhood AIS. The majority of results were descriptive (case studies, series, cohorts) as would be expected for a rare neurological condition. These demonstrate that immunotherapies are used in childhood AIS, commonly as steroids in children with
arteriopathy. However, with no internal controls or comparison groups they provide very weak evidence on the association between treatment and outcomes.

*Prevention:*

In previous AIS cohorts, estimates of recurrent stroke have varied from 1%-37%[4 7 8 55]. The higher rates of recurrence tend to be found in children with arteriopathies[7]. The cases in this review were predominantly arteriopathies, so arguably one might expect to see a high rate of recurrence here. However, contrary to this, there was a low rate of recurrence: only 1/37 (2.7%) in the individual cases, and none in any of the cohorts.

One possible explanation for the low recurrence found in this review is a publication bias. If cases with a good outcome were more likely to be written up by clinicians, this could lead to an underestimate of recurrence. However, this would not apply to the cohorts. Also publication bias may be more likely to go in the other direction: it is commonly the complex/severe cases that are written up as case studies, which would if anything lead to an overestimate of poor outcomes including recurrence.

The observation of low recurrence in this review is also consistent with, and perhaps sympathetic to the theory that the immunotherapy received by these children reduced the risk of recurrent AIS. This possibility is supported by the finding in both trials that children treated with steroids had reduced odds of recurrent stroke compared to those untreated. The key limitation of the trials is that they were underpowered to detect a statistically significant difference in recurrence.

*Treatment:*
Broader neurological outcomes in the cases here also appear positive when considered in the context of other AIS cohorts: the mortality rate in the cases found here was 5%, whereas the best estimate from prospective, population-based studies of childhood AIS is 10%[4]. Other cohorts have variously estimated between 4-15% mortality[2 3 56] although the study that found the lowest mortality may be vulnerable to sampling bias – as a study of patients in a paid-for US healthcare plan, it may under-represent poorer children and thereby underestimate poor outcomes. The cohorts in this review reported 0%, 4% and 21% mortality respectively, although the latter represented children with stroke in the context of bacterial meningitis, who may be expected to have particularly poor outcome. Direct comparisons are difficult due to selection biases that affect both systematic reviews, and some of the previous studies. However, results are consistent with the theory that immunotherapy has a neuroprotective role in treatment of acute AIS due to an inflammatory pathology. This possibility is given stronger support from the one trial that was adequately powered to detect statistically significant differences, which found that children treated with steroids had statistically significantly lower mortality, and improved cognition compared to those untreated.[53] The limitation of this trial was that the population was specifically children with Tuberculous Meningitis, who although at risk of AIS are not likely to be fully representative of AIS.

Overall this review found little robust evidence either in favour or against the use of immunotherapy in childhood AIS. There is weak evidence consistent with the hypotheses that in certain children at-risk, steroids may reduce the risk of recurrent stroke, and enhance neurological outcomes.
To our knowledge this is the first systematic review of the role of immunotherapies in childhood AIS. A strength of this review is the inclusive search criteria, which should have limited the possibility of missing any relevant evidence in an area with very little research so far.

A limitation is heterogeneity in the data. Due to the scarcity of the evidence, this review has grouped together cases of AIS with different aetiologies, which may be expected to vary in both treatment response and overall outcome. Also there may be variations in how clinicians classify severity of outcome. Points of homogeneity are that these were almost all cases of arteriopathy or acute infection, and mainly treated with steroids. Confounding by severity may also be affecting results: if the most severe cases tend to be treated with immunotherapy, then the prevalence of poor outcomes in the cases in this review will be overestimated.

The main challenge to interpretation is the scarcity of high-quality, analytic studies, which precludes firm conclusions on the efficacy of immunotherapies.

Several points justify further investigation of immunotherapy in childhood AIS. Firstly there is good theoretical basis for the hypothesis that immunotherapy could be an effective strategy, primarily to prevent recurrence, but also as a treatment in acute stroke to minimise neurological damage. Secondly although there is so far no strong positive evidence, the findings of this review are compatible with the concept of immunotherapy as an effective strategy in some cases. Specifically the findings were sympathetic to the hypothesis that steroids may be protective in cases of stroke with an infectious or inflammatory aetiology. Thirdly this review demonstrates that children with or at risk of AIS are being treated with
immunotherapies, and this practice should either be encouraged or discouraged on the basis of better evidence.

There is recent consensus among experts that the most important RCT to be undertaken in the field of child stroke is a trial of steroids in AIS.[39] We suggest that as the evidence so far is unclear, and as steroids are being used in some cases with uncertain benefit, a trial to determine safety and efficacy is justified. The most appropriate target group is likely to be children with arteriopathy, as this is the aetiological group most commonly treated in the literature and the group with most theoretical chance of benefit. The primary outcome should be preventing recurrent AIS, and secondarily measuring the effect on general neurological outcomes at a minimum of 12 months. A multicentre collaboration would be crucial to achieve sufficient recruitment.

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FO conceived the idea for the review and supervised all aspects of the work. HE, AAM and FO formulated the search strategy and design of the review. HE carried out the search, screening, data extraction, analysis and drafted the manuscript. FO and AAM contributed to the draft of the manuscript and all authors approved the final version.

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DISCLOSURES:

None.

What is already known on this topic:

- Little is known about the prevention or treatment of arterial ischaemic stroke (AIS) in children.
- Theoretically, immunotherapy may reduce the risk of occurrence/recurrence of AIS in cases of arteriopathy. It may also help limit neurological damage in acute AIS.
- Adult trials of steroids in AIS do not give consistent results, and cannot be generalised to children.
- There is expert consensus that the most important trial to be undertaken is an RCT of steroids in childhood AIS.

What this study adds:

- Steroids are used to treat children with AIS, particularly those with an infectious/inflammatory aetiology.
- Although the data is consistent with benefit in some children, so far there is no robust evidence on whether or not treatment is associated with better outcomes.
Treatment of childhood AIS should be based on more robust evidence from a randomised controlled trial.

REFERENCES


**FIGURE LEGENDS**
Figure 1: Flow chart of results included/excluded

Figure 2: Aetiologies of childhood AIS treated with immunotherapy

Figure 3: Immunotherapies used in childhood AIS

Figure 4: Neurological outcomes in immunotherapy-treated childhood AIS
Records identified through database searching (n=432) and references of relevant papers (n=83) (total n=515)

Records in title/abstract screening (n=515) → Records excluded (n=388)

Records in full-text screening (n=127) → Records excluded (n=80)

Records included (n=47) → Records excluded as related to systemic disease (n=13)

Total records included (n=34)
Number of cases by aetiology

- Idiopathic
- Meningitis
- West Nile Virus
- Henoch-Schönlein purpura
- Congenital toxoplasmosis
- Adenoviral infection
- Trauma
- Herpes Zoster Ophthalmicus
- Focal cerebral arteriopathy
- cPACNS (small vessel)
- cPACNS (medium/large vessel)
- VZV

*Individual data n=37, excludes cohorts and RCTs*
Number of times each immunotherapy was used

- Methotrexate
- Mycophenolate
- Intravenous Immunoglobulin
- Azathioprine
- Corticosteroids (unspecified)
- Prednisolone
- Cyclophosphamide
- Dexamethasone
- Steroids (unspecified)
- Methylprednisolone
- Prednisone

*Individual data n=37, excludes cohorts and RCTs*
Neurological Outcomes

- Not known
- Death
- Severe residual deficits
- Moderate residual deficits
- Mild residual deficits
- Complete recovery

*Individual data n=37, excludes cohorts and RCTs*
### Appendix A: Further individual data

(a) Cases with a presumed infectious/inflammatory aetiology:

<table>
<thead>
<tr>
<th>Case ID</th>
<th>Paper Year</th>
<th>Main suspected aetiology</th>
<th>Small/Large Vessel arteriopathy</th>
<th>Child age (years)</th>
<th>Gender</th>
<th>Immunotherapies used</th>
<th>Follow up (months)</th>
<th>Recurrence</th>
<th>Outcome / Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>Kutlesa 2009</td>
<td>Adenoviral infection</td>
<td>Large</td>
<td>4</td>
<td>M</td>
<td>Corticosteroids (unspecified)</td>
<td>1</td>
<td>No</td>
<td>Moderate deficits (motor)</td>
</tr>
<tr>
<td>1</td>
<td>Abe 2006</td>
<td>CNS Vasculitis</td>
<td>Large</td>
<td>12</td>
<td>M</td>
<td>Prednisone</td>
<td>36</td>
<td>No</td>
<td>Severe residual deficits</td>
</tr>
<tr>
<td>31</td>
<td>Salih 2006</td>
<td>Congenital toxoplasmosis</td>
<td>Large</td>
<td>3 days</td>
<td>M</td>
<td>Prednisolone</td>
<td>58</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>Bitter 2006</td>
<td>cPACNS</td>
<td>Large</td>
<td>5</td>
<td>F</td>
<td>IV Cyclophosphamide, IV Methylprednisolone, Oral Cyclophosphamide, Prednisone</td>
<td>108</td>
<td>No</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>30</td>
<td>Rosati 2013</td>
<td>cPACNS</td>
<td>Large</td>
<td>6</td>
<td>F</td>
<td>Prednisone, Steroids (unspecified), Mycophenolate</td>
<td>6</td>
<td>No</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>8</td>
<td>Bitter 2006</td>
<td>cPACNS</td>
<td>Small</td>
<td>7</td>
<td>F</td>
<td>Dexamethasone, IV Cyclophosphamide, Prednisone</td>
<td>14</td>
<td>No</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>16</td>
<td>Gallagher 2001</td>
<td>cPACNS</td>
<td>Large</td>
<td>7</td>
<td>F</td>
<td>Dexamethasone, Prednisone, IV Cyclophosphamide, Azathioprine, Methylprednisolone, Cyclophosphamide</td>
<td>12</td>
<td>No</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>17</td>
<td>Gallagher 2001</td>
<td>cPACNS</td>
<td>Large</td>
<td>8</td>
<td>F</td>
<td>Prednisone, Methylprednisolone, IV Cyclophosphamide</td>
<td>12</td>
<td>No</td>
<td>Moderate deficits (behavioural)</td>
</tr>
<tr>
<td>15</td>
<td>Gallagher 2001</td>
<td>cPACNS</td>
<td>Large</td>
<td>11</td>
<td>M</td>
<td>Methylprednisolone, Prednisone, IV Cyclophosphamide, Methotrexate</td>
<td>21</td>
<td>No</td>
<td>Mild deficits (motor)</td>
</tr>
<tr>
<td>38</td>
<td>Volcy 2004</td>
<td>cPACNS</td>
<td>Large</td>
<td>16</td>
<td>F</td>
<td>Steroids (unspecified)</td>
<td>NR</td>
<td>No</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>37</td>
<td>Volcy 2004</td>
<td>cPACNS</td>
<td>Large</td>
<td>18</td>
<td>M</td>
<td>Steroids (unspecified)</td>
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<td>Immunotherapies used</td>
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i. As described by original report authors

(b) Cases without a presumed infectious/inflammatory aetiology:

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<th>Case ID</th>
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<th>Child age (years)</th>
<th>Gender</th>
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</table>

i. As described by original report authors

iii. NR = not reported