Proposal of high dose intravenous immunoglobulin as a treatment for severe cases of tick-borne encephalitis

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Abstract

Background - Arthropod-borne viral encephalitis of diverse origins shows similar clinical symptoms, histopathology and magnetic resonance imaging, indicating that the pathomechanisms may be similar. So far, there is no specific therapy for them. Vaccination remains the best prophylaxis against some of them. However, there are increasing numbers of case reports on the successful treatment of arboviral encephalitis with high dose intravenous immunoglobulins.

Discussion - To our knowledge, high dose intravenous immunoglobulin has not systematically been tried for the treatment of severe cases of tick-borne encephalitis. Antibody-dependent enhancement has been suspected, but not proven, in several juvenile cases of tick-borne encephalitis. Although antibody-dependent enhancement during secondary infection with dengue virus has been documented, no adverse effects were noticed in a controlled study of high dose intravenous immunoglobulin therapy for dengue-associated thrombocytopenia. The inflammation-dampening therapeutic effects of generic high dose intravenous immunoglobulins may override the antibody-dependent enhancement effects potentially induced by cross-reactive antibodies or by virus-specific antibodies at sub-neutralizing levels.

Summary - In analogy to the increasing number of case reports on the successful treatment of other arboviral encephalitides with high dose intravenous immunoglobulins, it is proposed to treat also severe cases of tick-borne encephalitis with high dose intravenous immunoglobulins as early in the disease course as possible.

Keywords

arboviruses; T-cell; inflammation; MRI; macrophage; neopterin; TBE; tick-borne encephalitis; T2-weighted hyperintensity

Background

Tick-borne encephalitis (TBE): epidemiology, radiologic findings and pathology - Together with other prominent human pathogenic arthropod-borne (arbo) viruses, such as yellow fever virus (YFV), dengue virus (DENV), Japanese encephalitis virus (JEV), West-Nile virus (WNV) and other less known relatives, the
The tick-borne encephalitis virus (TBEV) belongs to the Flaviviridae family (for review see [1]). Flaviviruses are enveloped viruses with a single-stranded RNA in positive-strand orientation. Three TBEV subtypes, namely the European, the Siberian and the Far-Eastern subtype, are endemic in different greater geographical areas in Europe and Asia. The Western TBEV subtype is mainly transmitted by the tick species *Ixodes (I.*) ricinus*, the Eastern subtypes mainly by the tick species *I. persulcatus* from rodents and other small mammals. Vaccination is highly effective in preventing TBE disease and is recommended for persons who are exposed to TBEV in endemic areas [2].

After an incubation period of one or two weeks (4 to 28 days), the typically biphasic febrile disease involves a flu-like illness of four (1 to 8) days at first, during which the virus becomes viremic, and secondly the invasion of the entire reticulo-endothelial system and the central nervous system (CNS) after a lag period of one week (1 to 33 days). The virus is neurotropic and causes meningitis, meningoencephalitis, meningoencephalomyelitis or meningoencephalomyeloradiculitis, and may result in long-lasting or permanent neurological damage, a so-called post-encephalitic syndrome. In recent years, between 2,000 and 4,000 clinical cases were reported annually for Europe without the European parts of Russia and Asia [1,3]. Since mild flu-like only disease occurs more frequent (an estimated 70 to 80 % of cases) than neurological disease, the real case numbers are estimated to be much higher than the reported ones [3]. In slightly more than half of the reported clinical cases, full recovery takes place, slightly less than half of the patients are afflicted with residual sequelae, and the disease is fatal in less than 1 % of European subtype TBE cases. The lethality of the two Eastern TBEV subtypes is higher [1]. In elder patients, severe disease courses are more frequent than in children, but severe courses also occur in children (for review see [4,5]). It has not been systematically resolved, whether antibody-dependent enhancement (ADE) may have taken place in some childhood TBE cases after post-exposure prophylaxis [6-8], as it has been described for secondary DENV infection. While enhancement was observed in cell culture [9], it has not been found in TBE-infected mice, after passive pre- or post-exposure prophylaxis had been given [10].

Widespread lesions in the CNS may involve gray matter and leptomeninges of the brain stem, medulla oblongata, nuclei, cerebellum and spinal cord (for review see [4,5]). A prominent perivascular infiltration by activated inflammatory cells such as macrophages and leukocytes is observed. Furthermore, neuronal degeneration,
necrosis and neuronophagia occur. Elevated intrathecal neopterin which is secreted by stimulated macrophages, indicates a high degree of macrophage and T-cell activation [11]. Magnetic resonance imaging (MRI) is normal in the majority of cases [12]. However, enhanced signals in T2-weighted MRI scans have been regularly observed in the acute phase of severe TBE [13] and sometimes for extended time periods in protracted disease courses [6,8]. MRI demonstrated CNS damage mainly in the thalamus, cerebellum, nucleus caudatus and the brain stem [14].

The mechanisms by which TBEV causes encephalitis are not completely understood, but a composite of direct cytolytic viral damage and of considerable immune pathology is likely. Mouse models of TBE disease demonstrated that immune pathology contributed significantly to the neurological damage in TBE [15]. While normal mice succumbed to the CNS inflammation caused by TBEV infection, CD8-knockout mice or mice with a severe combined immune deficiency (SCID) exhibited prolonged survival. On the other hand, the adoptive transfer of CD8+ T-cells to infected SCID mice, significantly shortened their survival, while the transfer of CD4+ T-cells prolonged their survival. The viral load was the same in normal mouse strains and in CD8-knockout mice, while it was higher in SCID mice. The histological brain lesions were more moderate in immune suppressed mouse strains than in immunocompetent mice. Inflammatory infiltrates around meningeal vessels consisted mainly of CD8+ T-cells, and contained also histiocytes, but little CD4+ T-cells. These experiments proved a key role for the CD8+ T-cells in the pathology of TBE, and that TBE is essentially an immunopathological disease [15]. Moreover, experimental immune suppressive therapy with cyclophosphamide led to an increased survival time of TBEV-infected mice [16]. The CNS pathology induced by other flaviviruses, such as WNV and Murray Valley encephalitis virus, was also more caused by the immune system than by cytolytic virus replication. Like in TBE, CD8+ T-cells were the main culprits of the immune damage caused by WNV, while CD4+ T-cells prolonged the survival of WNV infected mice [15,17]. However, contrary to TBE, where the viral load was not correlated with the presence or absence of CD8+ T-cells, WNV load was lower in immunocompetent mice. Both in TBEV and WNV encephalitis, CD8+ T-cells were required for the eventual clearance of WNV from the organism and for mouse survival [15,18]. This shows that part of the neuronal damage is also directly due to virus infection [15,19]. Thus, the mouse experiments indicate that an immunomodulatory treatment which dampens the inflammatory immune response,
while not disabling it, may help curbing flaviviral CNS pathology. A case in point was the quicker recovery of TBE patients from their clinical symptoms who were treated with the immunomodulatory antibiotic tetracycline which reduced the inflammatory response [20].

Currently, there is no specific treatment available for TBEV-disease. However, since immune modulation by tetracycline was helpful, immunomodulatory therapy may be the way to go for [20]. Ideal therapy would embrace three roles: the enhancing of protective immune reactions, the normalization of immune regulation, and the suppression of the damaging mechanisms of immune response. A well-proven option of immune modulation is the administration of generic high dose intravenous immunoglobulins (IVIG) at 1 to 2 grams per kilogram body weight over a time course of 2 to 5 days, like it is given for several acute hyperinflammatory autoimmune conditions, e.g. Kawasaki vasculitis, Guillain-Barré syndrome, myasthenia gravis, immune thrombocytopenia, macrophage activation syndromes, or may also be given as an adjunctive therapy for sepsis. The best known effects of high dose IVIG are (i) blockade of the Fc receptors of macrophages and thereby blockade of the clearance of antibody coated cells in the reticuloendothelial system, (ii) blockade of complement activation through the abrogation of the ability of aggregated antibodies to lead to complement activation, and also through scavenging of complement components, (iii) specific neutralization of pathogens by anti-pathogen antibodies present in the mixture. (iv) The mechanisms of reducing inflammatory cytokines, suppressing T-cell responses and dampening inflammatory reactions in general are not entirely clear yet [21-23].

Discussion

Since the neuropathological and neuroradiological findings in various arboviral encephalitides are of similar nature and therefore non-specific [13,24], it is interesting to note a series of case reports on the successful intervention with high dose IVIG in severe cases of viral encephalitis of arboviral origin other than flaviviruses and of flaviviral origin other than TBEV. However, the early intervention with high dose IVIG in severe TBE cases has, to our knowledge, not been reported so far. The following case reports are grouped together with respect to the viral cause.
**Tick-borne encephalitis virus** - After complete vaccination and two times booster against TBE the last one of which he had received 39 months before, a 54 year old man came down with a severe and complicated TBE. After two weeks the patient developed sinus tachycardia, hypertonia and gastrointestinal tract dysfunction. These symptoms and a fixed heart rate were taken as signs of autonomic failure. Late after onset, i.e. from day 20 to 24 of his illness, the patient received high dose IVIG at a dose of 0.4 grams per kilogram body weight each day. While the dysautonomic symptoms improved and cardiac arrhythmia disappeared, the other neurologic symptoms did not change, and a post-encephalitic syndrome persisted which forced the patient into early retirement [25]. In this context, it may be interesting to note that actual IVIG preparations contain very different levels of anti-TBE antibodies, dependent on their geographical origin [26].

**Japanese encephalitis virus** - JEV is the most common cause of mosquito-borne flaviviral encephalitis in Asia. 30,000 to 50,000 cases are reported annually. Contrary to TBE, mortality is high in the range of 25 to 30%. Sequelae are observed in about 50% of those who survive [27,28]. A 49 year old Italian traveller to Vietnam with a severe form of JE showed extensive T2-weighted hyperintensities in the MRI scan. T2-weighted hyperintensities have also been described in other JE cases [24,29]. Diagnosis was established by JEV-specific antibodies in CSF and serum. The patient was treated symptomatically, but his condition worsened, when on the sixth day a five day course of IVIG at a dose of 0.4 grams per kilogram body weight each day was started. It was not reported whether the applied IVIG preparation contained specific anti-JEV antibodies. Beginning with the next day, his condition started to improve. After three weeks he was discharged home with slight symptoms of speech, motor and mental activity remaining, but with a normal MRI. One month after discharge, only a slight deficit in recent memory was observed [27,28].

In addition to hypotension, respiratory failure and general meningoencephalitic symptoms, a 64 year old man with JE had prominent signs of parkinsonism. MRI scans showed T2-weighted hyperintensities in the thalamus and substantia nigra corresponding to those signs of parkinsonism. A more than four-fold increase of specific antibodies against JEV proved the cause of his disease. A total of 40 grams of IVIG containing anti-JEV antibodies was administered in two courses separated by one month. His symptoms ameliorated after each course. Although there were
residual symptoms on discharge to rehabilitation, the treatment was thought to have saved the patient’s life [29].

**Dengue virus** - DENV comes with four subtypes and is known for more severe disease courses upon secondary infection. In such cases, a frequently observed symptom is a pronounced thrombocytopenia leading to haemorrhage which is likely due to bone marrow infection and, in addition, possibly due to the clearance of thrombocytes through macrophages. Worldwide, more than 1,000 deaths occur annually due to dengue haemorrhagic fever [30]. An increased level of platelet-associated IgG is frequently observed in dengue haemorrhagic fever. A randomized controlled study with 31 cases of secondary DENV infection in the Philippines compared the effect of early intervention with high dose IVIG versus non-intervention on platelet recovery. Beginning with the second day of their hospital stay, IVIG was given to 15 patients at a dose of 0.4 grams per kilogram body weight each day for a three day course. It was not reported whether the IVIG-preparation (Gammmamune, Bayer Health Care, Brea, California) contained anti-DENV antibodies. There was no effect on platelet recovery. The authors concluded that platelet clearance by macrophages through Fcγ-receptors is not the primary mechanism causing thrombocytopenia in this disease. However, an adverse outcome associated with the IVIG treatment was not observed in any of the IVIG-treated cases [30]. This indicates that the administered IVIG did not cause ADE, although enhancement has been shown to occur after secondary DENV infection, mainly with another subtype [2,30]. Dengue infection can also cause a variety of neurological complications which may result in poor recovery and long-term disability. It remains to be studied, whether the rare case of DENV encephalitis or encephalopathy would respond to high dose IVIG. The conduction of randomized clinical trials investigating the potentially beneficial effects of IVIG for the various life-threatening manifestations of dengue fever has been proposed [31].

**West Nile virus** - WNV is originally endemic in the Middle East. Beginning with a couple of cases in New York City, WNV has conquered the USA from East to West Coast through a bird, horse, mosquito and human-cycle between the years 1999 and 2002. WNV disease including neurological involvement has a high mortality in the range of 5 to 14 % [32,33]. Eight cases of WNV encephalitis were treated with
high dose IVIG at a dose of 0.4 grams per kilogram body weight each day for a five
day course. The blood used for this IVIG preparation (Omdra Biopharmaceuticals Ltd.,
Israel) had been donated by healthy anti-WNV seropositive Israeli donors and
therefore contained high levels of specific anti-WNV antibodies. Disease courses
were severe. Four patients needed mechanical ventilation. MRI scans were not
systematically done. Six of the eight patients improved significantly upon the high
dose IVIG treatment and could be discharged home, while two patients died from
their disease. One of the patients who died, had a kidney transplant and was immune
suppressed. The earlier the immunoglobulin treatment was started, the faster was the
improvement of the neurological symptoms. The two patients who died, received high
dose IVIG later than the fifth day of their disease. The authors concluded that the
early administration of anti-WNV hyperimmune high dose IVIG should be
recommended for WNV encephalitis [33].

Acute flaccid paralysis is a life-threatening complication of WNV infection. A 55
year old man with a quickly developing muscle weakness, reaching his respiratory
muscles on the third day so that the patient needed mechanical ventilation was
suspected to have a Guillain-Barré syndrome. Dexamethasone and plasmapheresis
were administered. When on the sixth day WNV was suspected, corticosteroids and
plasmapheresis were discontinued, and anti-WNV hyperimmune high dose IVIG at a
dose of 0.4 grams per kilograms body weight each day for a seven day course was
started instead. This treatment led to the rapid improvement of his muscle weakness,
so that the patient could be discharged to inpatient rehabilitation after one month
[34]. Since the WNV diagnosis was established on the basis of an anti-WNV IgM in
the serum, but IgG was not reported, it can formally not be excluded that the IgM
might have been a non-specific reactivity, and the acute flaccid paralysis might
actually have had a different cause than WNV, although the diagnosis seems most
likely correct.

There are additional cases of WNV encephalitis successfully treated with anti-
WNV hyperimmune high dose IVIG [35-39]. A remarkable WNV case report including
a review of the literature was presented by Rhee et al. (2011). That case is unusual,
because the infection was transmitted through a transplanted liver. When WNV was
suspected in this case, serum was taken for analysis and the patient received 0.4
grams of anti-WNV hyperimmune IVIG per kg body weight each on the fourth and
eighth day of his hospital stay and recovered fully. On the fifth day, a positive IgM
both in serum and CSF samples which had been obtained before the start of IVIG, and the MRI scans pointed to WNV. Final proof came through a positive WNV-PCR from a retained blood sample of the liver donor who had not shown any WNV-typical symptoms at the time of his death through intracranial haemorrhage during a hypertensive crisis [39].

WNV with the highest number of case reports of arboviral encephalitis treated with high dose IVIG is special, because anti-WNV hyperimmune IVIG preparations are available. This means that, besides the immunomodulatory effects of generic high dose IVIG which is dampening hyperinflammatory states without a noteworthy accompanying immune suppression, there is also a specific protective anti-WNV effect exerted by those immunoglobulin preparations [40].

**Eastern Equine encephalitis virus** - EEE is caused by EEE virus, a member of the Alphavirus genus, family *Togaviridae*. EEE, with a mortality of about 30 %, is the most severe of the mosquito-borne encephalitides. Age over 40, rapid progression to coma, severe hyponatremia, and a CSF white blood cell count above 500 at symptom onset have all been correlated with poor outcome [41]. A 69 year old man with rapidly progressing EEE showed extensive T2-hyperintensities in repeated MRI scans and became comatose on the third day of his illness. On the third day of his hospital stay, one gram of methylprednisolon per day was started and slowly tapered. The diagnosis was established by EEEV-specific antibodies in the CSF and serum. Beginning with the fifth day, the patient was given a total of 210 grams of generic IVIG over five days. It was not reported whether the applied IVIG preparation contained anti-EEEV antibodies. Beginning with the sixth hospital day, his condition started to improve. After more than two months, he was discharged home with few and relatively mild remaining symptoms, such as mild inattention, bradykinesia, short-term memory impairment, and emotional lability, all of which resolved during the following year [41].

**Chikungunya virus** - CHIKV is a mosquito-borne virus belonging to the genus Alphavirus, family *Togaviridae*. CHIKV typically causes a febrile disease in Africa and South-East Asia which is characterized by severe joint pain and can become haemorrhagic and cause encephalitic symptoms in rare cases. The virus has been imported to Europe through international travel, and outbreaks have already occurred
in Europe, e.g. in Northern Italy. Three cases with neurological symptoms are reported by Chusri et al. (2011). The cases showed hyperintense signals in the MRI scan. Patient 1 was a 27 year old woman who recovered on supportive measures. Patient 2 was an 85 year old man who had not recovered at follow-up one year later. Patient 3, a 44 year old woman, who suffered a very severe form of late onset CHIKV encephalitis, was given a four day course of high dose IVIG and recovered quickly upon administration of the immunoglobulins and had recovered completely at follow-up after six months. It was not reported whether the IVIG preparation contained anti-CHIKV antibodies [42].

**Acute disseminated encephalomyelitis and other viruses** - ADEM is an autoimmune phenomenon which may be triggered by infections or rarely even by vaccinations and has a similar clinical appearance as viral encephalitis. Essentially, the diagnosis of ADEM is based upon a combination of clinical and radiologic features and the exclusion of specific diseases that resemble ADEM. MRI scans again show disseminated T2-weighted hyperintensities [43,44]. Three cases on the successful treatment of ADEM with high dose IVIG were reported by Nishikawa et al. (1999). Although in most cases of ADEM the trigger remains obscure, a mumps virus infection was found to be the cause for post-infectious ADEM in the third of the described cases [45].

High dose IVIG has been reported to play an advantageous role also in the treatment of encephalitis induced by other viruses. Two severe cases of influenza A virus-induced encephalitis responded very favourably [46,47]. Furthermore, a case of brainstem encephalitis induced by herpes simplex virus type I in an adult was effectively treated with a combination of high dose aciclovir, steroids and IVIG [48]. Also for the treatment of 55 children with prior malignant disease who suffered severe enteroviral complications which included five cases of encephalitis, early high dose IVIG has been reported to lead to a negative viral load faster. Thus, early intervention was recommended in order to improve the clinical outcome [49]. Another controlled trial including 18 confirmed cases of enteroviral encephalitis reported favourable clinical results after the early intervention with one gram IVIG per kilogram body weight [50].
**Adverse effects of high dose IVIG** - The diverse case reports discussed above suggest that the early intervention with high dose IVIG may be a general treatment option for viral and post-infectious encephalitides. Although IVIG is generally well tolerated, it is not free of side effects. Adverse effects are mostly mild and include headache, fever, nausea, diarrhoea, blood pressure changes and tachycardia. More severe adverse effects include renal failure, thromboembolic events and anaphylactic reactions which are related to IgA-deficiency. The prior exclusion of an IgA deficiency and the slow administration of IVIG in a sufficiently large liquid volume helps minimizing the serious side effects [23].

**Antibody dependent enhancement** - With the exception of secondary DENV infection, ADE of flavivirus infection is without clear and systematic proof in vivo and still under debate. Enhancement was not observed in TBE-infected mice [10], although it was seen in cultured macrophages or monocytes in vitro [9]. However, when a couple of very severe childhood TBE cases had been observed after the administration of specific hyperimmune serum to non-vaccinated children after tick bites [6-8], passive post-exposure prophylaxis for non-vaccinated persons was discontinued as a cautionary measure and never re-introduced again. ADE of DENV infection of Fcγ-receptor bearing cells has been ascribed to cross-reactive non-neutralizing antibodies or to neutralizing antibodies at sub-neutralizing levels [2]. This may be due to the intermediate genetic distance of 60 to 75 % at the amino acid level between the four DENV subtypes. Except for the tick-borne flaviviruses Powassan and TBE virus which have an intermediate genetic distance of about 75 %, the genetic similarity between TBEV and the mosquito-borne flaviviruses is below 50 % [1]. Thus, cross-enhancement should not occur between mosquito-borne flaviviruses and the TBE virus. Even if ADE might be operative in TBE under rare circumstances, e.g. after prior infection with WNV [51] or after vaccination against YF, both of which is unlikely, or during infection at sub-protective levels of anti-TBE antibodies, which anecdotally may have been observed [6-8], these enhancing effects should most likely be overridden by the anti-inflammatory action of high dose generic IVIG. As a case in point, transiently immune suppressed mice were not harmed by the administration of specific anti-TBE antibodies. To the contrary, under transient immune suppression, serotherapy became more efficient and mostly prevented persisting infections [52].
Summary

Active anti-TBEV vaccination continues to be the mainstay of TBE prophylaxis [2]. However, even with a high overall vaccination rate, some TBE cases experiencing a severe disease course will remain. To our knowledge, early intervention with high dose IVIG has not been reported for TBE. Therefore, we suggest trying it on presumably desperate cases and conducting a randomized controlled study on a small number of such severe cases. In analogy to anti-WNV hyperimmune IVIG, it may be important to obtain immunoglobulins from blood donors vaccinated against TBE [26]. It may be reasonable to develop IVIG which contain a high level of anti-TBE antibodies. Clinical symptoms, CSF laboratory parameters including neopterin, together with a characteristic acute phase MRI may allow a tentative diagnosis very early, even before serological test results are returned, and may indicate the early intervention with high dose IVIG.

List of abbreviations used

ADE, antibody-dependent enhancement; ADEM, acute disseminated encephalomyelitis; arbo, arthropod-borne; CHIKV, Chikungunya virus; CNS, central nervous system; CSF, cerebrospinal fluid; DENV, dengue virus; EEEV, Eastern Equine encephalitis virus; IVIG, intravenous immunoglobulin; JEV, Japanese encephalitis virus; MRI, magnetic resonance imaging; SCID, severe combined immune deficiency; TBE, tick-borne encephalitis; TBEV, tick-borne encephalitis virus; WNV, West-Nile virus; YFV, yellow fever virus.

Competing interests

none

Authors´ contributions

DR, GD and HHN: wrote the paper, read and approved the final manuscript; HHN: concept of the paper.

Authors´ information
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