Steroids and Childhood Encephalitis

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Glucocorticosteroids (GS) have both anti-inflammatory and immunosuppressive property, which explains why pediatricians tend to prescribe them for all pediatric clinical conditions in which it is thought or known that inflammation and/or autoimmunity are the main cause of disease signs and symptoms. However, such prescriptions are sometimes questionable because the efficacy of GS has not been demonstrated by controlled trials, and the risk of adverse events following high-dose or prolonged administration has not been adequately evaluated.

Encephalitis is one of the syndromes for which GS are frequently used. However, the importance of this treatment remains unclear because a diagnosis of encephalitis covers a range of clinical conditions whose etiology, pathogenesis, clinical picture and spontaneous evolution vary. Furthermore, it has been tested in very few studies involving children.

The aim of this article is to review what is currently known about the real impact of GS treatment in children with acute infectious encephalitis (AIE) and acute disseminated encephalomyelitis (ADEM), the 2 major types of encephalitis.

**ACUTE INFECTIOUS ENCEPHALITIS**

The neurological signs and symptoms of AIE usually occur within a clinical picture that is characteristic of the infectious agent causing central nervous system (CNS) involvement which, in most cases, can be found in the CNS, other sites of the body or biological fluids. Viruses are the most frequently identified. Since the implementation of vaccination programs that have eliminated or significantly reduced the circulation of measles, mumps and rubella viruses in industrialized countries, herpes simplex virus (HSV, particularly type 1) is the most frequent cause, followed by virus varicella zoster (VZV; in countries where VZV vaccination coverage is low). However, pathogens such as Mycoplasma pneumoniae, Japanese encephalitis virus, enteroviruses and tickborne encephalitis virus have also been identified. In addition, some bacteria (mainly Streptococcus pneumoniae and Neisseria meningitidis) may cause AIE usually secondary to meningitis.

GS have a great potency to limit inflammation, and their use could modulate the enhanced inflammatory response observed during serious infections. The use of GS to treat childhood AIE has never been studied in controlled trials, and it is not officially recommended because of concerns that their immunosuppressive activity may increase viral replication and spread. However, this may not be true in the case of HSV CNS infection, because they only slightly delay virus clearance and do not limit the acyclovir-induced inhibition of viral replication in experimental animals.

Moreover, as the CNS signs and symptoms following HSV infection are not only due to direct virus-mediated tissue damage but also due to an autoimmune mechanism, it is possible that GS may have a beneficial effect on the evolution of HSV AIE. Experimental data indicate that they may attenuate CNS damage by reducing cytotoxic and prostaglandin production, and limiting the nitric oxide concentration induced by the increased expression of immunological nitric oxide synthase. Furthermore, in HSV-infected mice, methylprednisolone significantly reduces long-term magnetic resonance imaging abnormalities, and dexamethasone restricts neuronal cell death.

Similar positive effects have been found in human studies, although most of these were retrospective studies of adults. In general, adults treated with GS plus acyclovir had a better outcome than those receiving acyclovir alone because they survived without sequelae or with only minor CNS damage, and did not experience any major GS-related adverse events. Positive results have also been described in pediatric case reports.

The optimal timing of GS administration in HSV AIE has not yet been defined. However, although GS were prescribed simultaneously with acyclovir in most published cases with a favorable evolution, animal and human data suggest that neurological signs and symptoms can still improve if GS are started some days or even more than 2 weeks after disease onset. No data in favor of GS use are available from studies performed in neonates.

Optimal doses and treatment duration are also unclear and related to the used agent. Musallam et al. used pulsed methylprednisolone at a dose 1 g/1.73 m² for 3 days, but high-dose dexamethasone could be administered for the same period.

In conclusion, although they are interesting and encouraging, the available data are too limited to support an official recommendation for the systematic use of GS in HSV AIE, and only antiviral therapy can be universally suggested. The results of a currently ongoing randomized controlled trial in Europe should provide information that may allow a more precise evaluation, but in the meantime it can be suggested that treatment with GS may be attempted in cases in which antiviral therapy does not seem to control the clinical picture of HSV AIE, and CNS damage is clearly increasing on the basis of clinical findings and neuroimaging.

Similar conclusions can be drawn in the case of AIE associated with VZV infection because, once again, the neurological damage is at least partially attributable to an immune mechanism that may be reduced by GS administration. In adults, expert opinion suggests administering GS in AIE associated with VZV reactivation, particularly if nuclear magnetic resonance imaging suggests a stroke secondary to large vessel vasculitis. The suggested dose is 60–80 mg of prednisolone (2 mg/kg/day in children) once daily for 3–5 days, but no controlled trial supports this recommendation.

GS do not seem to be effective in AIE associated with Japanese encephalitis virus infection, and no conclusive data are available concerning their effect on in AIE due to other infectious agents.

**ACUTE DISSEMINATED ENCEPHALOMYELITIS**

ADEM is mainly diagnosed in children and has an estimated incidence of 0.8/100,000 per year. It is classified as a demyelinating disease of the CNS and is a condition that may be regarded as a bridge linking neurology and the infectious diseases. The clinical features and history of the disease create difficulties in differential diagnosis both with encephalomyelitis caused...
by infectious agents and with noninfectious inflammatory diseases (other demyelinating syndromes, vasculitis, nonvasculitic autoimmune encephalopathies). Recurrent ADEM has been described, but in most cases it is a monophasic inflammatory and demyelinating disease that usually occurs some days or weeks after an infection or a vaccination. Although not fully assessed in randomized, placebo-controlled trials, GS are generally recommended for children with ADEM, who are usually treated with methylprednisolone 10–20 mg/kg/day intravenously for 3–5 days followed by a tapered course of oral prednisolone. A number of authors have found that GS are immediately effective in most cases, leading to a clear improvement in neurological signs and symptoms after a few days of administration even in patients with protracted worsening before the start of treatment. Only a minority of children with ADEM seem to be refractory to steroid therapy and require the addition of immunoglobulins or the use of plasmapheresis.

The use of GS to treat ADEM is strongly suggested by the supposed pathogenicity of the syndrome itself. It is thought to be an autoimmune disease for which 2 pathogenic mechanisms have been proposed. The first is suggested by the similarity between the histological features typically found in biopsy and autopsy samples of ADEM patients and those found in animals with experimental autoimmune encephalomyelitis due to immunization with myelin proteins or peptides. As perivascular infiltrates of T cells and macrophages, associated with perivenular demyelination, are usually found in both cases, it has been suggested that in children with ADEM viral or bacterial epitopes resembling myelin antigens may activate myelin-reactive T-cell clones as a result of molecular mimicry, thus inducing a specific CNS response against the brain and spinal cord. This pathogenic hypothesis is further supported by the finding of high-affinity antibodies directed against myelin basic protein, a major component of myelin, in some patients diagnosed as having ADEM who had previously received rabies vaccination. The second hypothesized pathogenic mechanism in favor of GS administration is based on the consideration that a neurotropic infectious agent may damage the CNS and disrupt the blood/brain barrier, thus leading to a systemic leakage of CNS-confined autoantigens into the circulation. This might cause the breakdown of tolerance and cause the emergence of a self-reactive and encephalitogenic T-cell response, and the secretion of cytokines, chemokines or other soluble factors could perpetuate inflammation over time. There is no evidence in ADEM that there is a systemic inflammation that causes the clinical pattern.

In conclusion, unlike AIE, ADEM is a disease for which the available data seem to indicate the systematic use of GS. The possible relationships between ADEM and multiple sclerosis further support this recommendation, although there is not enough evidence to conclude that ADEM eventually leads to multiple sclerosis.

CONCLUSIONS

In conclusion, we do not support the systematic use of GS in AIE and we suggest that treatment with GS may be attempted in cases in which antiviral therapy does not seem to control the clinical picture of AIE, and CNS damage is clearly increasing on the basis of clinical findings and neuroimaging. On the contrary, ADEM is a disease for which the available data seem to indicate the systematic use of GS.

REFERENCES