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A) COMMENTS ON PUBLISHED ARTICLES

The role of interleukin 6 in the pathogenesis of hyponatremia associated with Guillain-Barré syndrome

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To the Editor,

We read with great interest the contribution by Monzón et al.[1] They reported a significant case of a man who had Guillain-Barré syndrome (GBS) with syndrome of inappropriate antidiuretic hormone (SIADH) and speculated that increased sensitivity to vasopressin in the renal tubule and a long-lasting hypo-osmolarity or antidiuretic substances might cause GBS-related SIADH. However, we would like to add a possible pathomechanism in the development of hyponatremia associated with GBS.

According to a previous study by Maimone et al.,[2] interleukin (IL)-6, a multifunctional cytokine, might be implicated in the immunopathogenesis of GBS. In their study, serum IL-6 levels were increased in six (26%) of 23 GBS patients, and detectable levels of IL-6 were also found in the cerebrospinal fluid in 13 (57%).[2] Using enzyme-linked immunospot assays, Press et al.[3] found elevated numbers of IL-6-secreting blood mononuclear cells during the acute phase in patients with GBS.

Quite recently and importantly, Swart et al.[4] depicted the cascade-like fashion of events initiated by an inflammatory stimulus (lipopolysaccharides), with tumor necrosis factor-α secreted first, IL-1β second, and IL-6 last, suggesting possible pathways connecting IL-6 to vasopressin release. These pro-inflammatory cytokines are secreted into the systemic circulation to initiate the acute phase response which is involved in the innate immune system.[5] Furthermore, Mastorakos et al.[6] reported that plasma antidiuretic hormone levels were elevated after IL-6 injection in cancer patients, suggesting that IL-6 activated the magnocellular ADH-secreting neurons and that it might be involved in SIADH. Activation of the subfornical organ and the organum vasculosum of the lamina terminalis by IL-6 could eventually lead to thirst and increased vasopressin secretion by neurons from the supraoptic nucleus and paraventricular nucleus.[4] The combination of antidiuresis and increased water intake may result in hyponatremia.

Therefore, there is a possibility that IL-6 may play a central role in the pathogenesis of hyponatremia associated with GBS. However, further studies are necessary to elucidate if IL-6 crosses the blood-brain barrier (BBB), or whether lipopolysaccharides cross the BBB and then increase IL-6 locally in the brain in the future.

Conflicts of interest

The authors declare they have no potential conflicts of interest related to the contents of this article.

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Acyclovir and valacyclovir neurotoxicity in patients with renal failure

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To the Editor,

It was with great interest that we read the article by Quiñones et al[1] in which they mention how toxicity secondary to starting new treatments in patients with renal failure can give rise to false diagnoses.

One of the patients cited by the authors suffered from neurotoxicity due to acyclovir. Acyclovir and its ester, valacyclovir, are widely used in treating infection with the varicella zoster virus,

and its Summary of Product Characteristics lists neurotoxicity as an extremely rare event. However, we have observed 3 episodes similar to that described by Quiñones et al in patients on haemodialysis receiving acyclovir-valacyclovir for metameric herpes zoster.

Case 1. Female patient aged 61 years treated with oral acyclovir at 800mg/12 hours. After the third dose, she experienced a psychotic reaction with visual hallucinations and dysarthria. Antiviral treatment was suspended and the psychiatric symptoms resolved completely in 3 days.

Case 2. Male patient aged 66 years undergoing treatment with oral valacyclovir (500mg/12 hours). After the second dose, he presented dysarthria and reduced consciousness. In light of a possible case of herpesviral encephalitis, treatment was changed to IV acyclovir at 400mg/day, with no noticeable response. The level of consciousness improved after each haemodialysis session, and then decreased again. When we suspected neurotoxicity caused by the antiviral agent, we reduced the acyclovir dose to 200mg/day and started daily haemodialysis sessions; the patient improved progressively and had recovered completely by the ninth day.

Case 3. Female patient aged 83 years who was treated with valacyclovir at 1g/12 hours as prescribed by her general practitioner. Dysarthria began following the third dose. Valacyclovir was suspended and the patient underwent daily haemodialysis during 3 days, the speech disorder resolving completely.

This last patient received a high dose of valacyclovir, but in the other two patients, acyclovir and valacyclovir doses were adjusted according to the stage of renal failure. A correlation between toxicity and plasma drug levels is under debate. Some authors state that there is a higher risk of toxicity when levels exceed 20 micromoles per litre,[2] but others claim not to have witnessed symptoms in patients with levels greater than 30 micromoles, and it is therefore impossible to establish a safe therapeutic range.[3] Furthermore, the early onset of the neurological symptoms was remarkable in our three cases: in all of the patients, symptoms appeared on the second day of treatment after the second or third oral dose, which would suggest that the cause was drug idiosyncrasy rather than drug accumulation.

Haemodialysis was effective in reducing the levels of acyclovir and its metabolites.[4] This is the most effective treatment for this type of neurotoxicity, and it is an important tool for the differential diagnosis of acyclovir neurotoxicity and viral encephalitis.[2,5]

The appearance of neurological or psychiatric changes in these patients should be taken into account in order to prevent misdiagnosis, as occurred in our own case 2 and in the case described by Quiñones et al.

Conflicts of interest

The authors declare they have no potential conflicts of interest related to the contents of this article.

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Estimating glomerular filtration rate in order to adjust drug doses: confusion abounds

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To the Editor,

Two recent events led to our writing this letter.

One. For 2 or 3 years now, our local biochemistry laboratories calculate the estimated glomerular filtration rate (eGFR) by means of the MDRD-IDMS formula (formerly MDRD) and the isolated creatinine value, as per National Kidney Foundation recommendations.[1]

Yet in October 2011, we still observe the following:

- The constant used by some biochemistry laboratories for the MDRD-IDMS formula is 186, when it should be 175 since the calculation for the serum creatinine value is standardised by IDMS.
- Some laboratories deliver MDRD-IDMS results in ml/min instead of ml/min/1.73 m^2. Although it is dependent on an individual's body surface area, this could lead one to