



## SCIENTIFIC LETTERS

## Activity of *Erwinia*-asparaginase after anaphylactic reaction to Peg-asparaginase<sup>☆</sup>



### Actividad de *Erwinia*-asparraginasa tras reacción anafiláctica a Peg-asparraginasa

Dear Editor:

L-Asparaginase (L-ASP) is one of the cornerstones of the treatment of paediatric acute lymphoblastic leukaemia (ALL).<sup>1</sup> It is used with the aim of depleting circulating asparagine, which induces apoptosis in malignant lymphoid cells indirectly by impeding protein synthesis.<sup>2</sup> This systemic depletion of asparagine requires an adequate level of L-ASP activity, which is currently considered to be a level exceeding 100 IU/L.<sup>3,4</sup>

Several L-ASP agents are currently available, each with different pharmacokinetic characteristics. Two are derived from *Escherichia coli*, including the enzyme in its native form (*E. coli*-ASP) and the pegylated enzyme (PEG-ASP); and 1 is derived from *Erwinia chrysanthemi* (*Erwinia*-ASP). Most current protocols recommend the use of the pegylated enzyme derived from *E. coli*, while the enzyme derived from *Erwinia* is used as second- or third-line treatment in cases of hypersensitivity, which develops in up to 22% of patients.<sup>5</sup> However, the hypersensitivity reaction is not the only response mediated by the immune system that limits the use of L-ASP, as the phenomenon known as silent inactivation has also been described in the literature (in 8%–10% of cases).<sup>2</sup>

Our aim in this work was two-fold: on one hand, we sought to demonstrate that routine measurement of L-ASP activity is feasible in everyday clinical practice in hospital settings, and on the other, to present a case that shows that it is possible to use *Erwinia*-ASP following a hypersensitivity reaction to PEG-ASP and to maintaining adequate activity levels as long as the dosing schedule established for this form of L-ASP is followed rigorously.

We present the case of a male patient aged 10 years with an ALL diagnosis that was treated according to the United Kingdom Acute Lymphoblastic Leukaemia (UKALL)

**Table 1** Trough values of plasma L-ASP.

Trough day	L-ASP (IU/L)
+2	385.14
+2	126.71 <sup>a</sup>
+3	28.83
+2	370.62
+2	221.05

L-ASP: L-asparaginase.

<sup>a</sup> Sample not stored under optimal conditions.

protocol. At 20 months, the patient experienced a relapse that was treated according to the 2015 LAL/SEHOP-PETHEMA protocol version 1.0 for a first relapse. The patient developed a hypersensitivity reaction following the initial dose of PEG-ASP, so, in adherence to current clinical guidelines, treatment was switched to *Erwinia*-ASP. Although the source of the protein was different, there was a risk of cross-reactivity that could involve either another hypersensitivity reaction or a silent inactivation of the new form of asparaginase. For these reason, we decided to monitor the levels of asparaginase activity at every through (every 48 h, [Table 1](#)).

The patient did not exhibit a hypersensitivity reaction after receiving the first dose of *Erwinia*-ASP. We only detected a suboptimal level of activity (<100 IU/L) in the third through (28.8 IU/L), which we attributed to a 24-h delay in the administration of the dose (at 72 h instead of 48 h) because it was Christmas day. The levels of activity returned to normal in subsequent cycles. Therefore, to date there is no evidence of silent inactivation taking place.

Our results show that *Erwinia*-ASP can be effective in the treatment of patients that have experienced a hypersensitivity reaction to PEG-ASP. Based on our experience, we can conclude that the use of *Erwinia*-ASP requires strict adherence to the administration of the drug every 48 h to ensure adequate levels of activity. To conclude, we would like to underscore that monitoring these levels makes it possible for clinicians to ascertain the correct use of asparaginase.

## References

- Pieters R, Hunger P, Boos J, Rizzari C, Silverman L, Baruchel A, et al. L-Asparaginase treatment in acute lymphoblastic leukemia. *Cancer*. 2011;117:238–49.
- Salzer W, Bostrom B, Messinger Y, Perissinotti AJ, Marini B. Asparaginase activity levels and monitoring in patients with acute lymphoblastic leukemia. *Leuk Lymphoma*. 2017;18:1–10.

<sup>☆</sup> Please cite this article as: Viña Romero MM, Gil SG, Casariego GJ, Alonso JM, Nicolás FG. Actividad de *Erwinia*-asparraginasa tras reacción anafiláctica a Peg-asparraginasa. *An Pediatr (Barc)*. 2019;90:187–188.

3. Moscardó Guilleme C, Fernández Delgado R, Sevilla Navarro J, Astigarraga Aguirre I, Rives Solà S, Sánchez de Toledo Codina J, et al. Update on L-asparaginase treatment in paediatrics. *An Pediatr (Barc)*. 2013;79:329.e1–11 [in Spanish].
4. Würthwein G, Lanvers-Kaminsky C, Hempel G, Gastine S, Mörcke A, Schrappe M, et al. Population pharmacokinetics to model the time-varying clearance of the PEGylated Asparaginase Oncaspar® in children with acute lymphoblastic leukemia. *Eur J Drug Metab Pharmacokinet*. 2017;42:955–63.
5. Tong WH, Pieters R, Kaspers GJ, te Loo DM, Bierings MB, van den Bos C, et al. A prospective study on drug monitoring of PEGasparaginase and Erwinia asparaginase and asparaginase antibodies in pediatric acute lymphoblastic leukemia. *Blood*. 2014;123:2026–33.

Maria Micaela Viña Romero<sup>a,\*</sup>, Sara García Gil<sup>b</sup>,  
Gloria Julia Nazco Casariego<sup>b</sup>, Javier Merino Alonso<sup>a</sup>,  
Fernando Gutiérrez Nicolás<sup>b</sup>

<sup>a</sup> Servicio de Farmacia, Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Tenerife, Spain

<sup>b</sup> Servicio de Farmacia, Complejo Hospitalario Universitario de Canarias, San Cristóbal de La Laguna, Tenerife, Spain

\* Corresponding author.

E-mail address: [kellyviro@gmail.com](mailto:kellyviro@gmail.com) (M.M. Viña Romero). 2341-2879/

© 2018 Asociación Española de Pediatría. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Fulminant acute cerebellitis: An under-diagnosed condition?☆



### Cerebelitis aguda fulminante, ¿una entidad infradiagnosticada?

Dear Editor:

Acute cerebellitis (AC) is an inflammatory syndrome that causes acute cerebellar dysfunction (ataxia, nystagmus or dysmetria) often in association with fever, headache, nausea and altered consciousness.<sup>1,2</sup> It usually occurs in the context of infection or after infection or vaccination, although there are cases in which a trigger is not identified.<sup>3–5</sup>

By consensus, cerebellar ataxia is defined as cases with normal neuroimaging, while AC is defined as cases presenting with imaging abnormalities,<sup>3</sup> and magnetic resonance imaging (MRI) is the gold standard of diagnosis. Computed tomography (CT) can be useful during the acute phase to rule out other aetiologies and to detect the development of acute hydrocephalus or severe compression of the brainstem.

Acute cerebellitis is an infrequent process and its diagnosis is challenging, as its presentation and course are widely heterogeneous. Early intervention is essential to optimise outcomes, so this disease should be suspected in patients with symptoms suggestive of posterior fossa involvement.

Cerebellar inflammation can lead to compression of the brainstem and cause alterations in the level of consciousness that may mask the initial manifestations of cerebellar involvement, as patients may even present with coma and autonomic dysfunction. This presentation, in which raised intracranial pressure (RICP) symptoms predominate over

cerebellar symptoms and associated with significant inflammation, is known as fulminant acute cerebellitis<sup>1</sup> and should be considered in the differential diagnosis of patients with RICP of sudden onset.<sup>1</sup> This form of disease carries an increased risk of permanent sequelae and even death.<sup>1,4,6</sup>

Due to the variable natural history of acute cerebellitis, its management needs to be individualised.<sup>4</sup> In mild cases without clinical progression or neuroimaging findings suggestive of a fulminant course, a conservative approach with close monitoring may be sufficient. In moderate to severe cases, steroid drugs are the first-line treatment to reduce the mass effect of inflammation, and placement of an external ventricular drain (EVD) may be necessary to manage hydrocephalus.

We now present the cases of 3 patients aged 7–12 years that received a diagnosis of AC, none of whom had a personal or family history of interest.

The first patient sought care due to vomiting and malaise, and presented on arrival with vasovagal syndrome, with altered level of consciousness, hypotonia and neurologic impairment. A cranial CT scan was performed, and the images showed hypodensity in the subcortical region of the left cerebellar hemisphere (Fig. 1A). The patient was admitted to the intensive care unit, and a cranial MRI was ordered to make the differential diagnosis between ischaemic injury of the posterior fossa, encephalitis and AC (Fig. 1B), while the patient remained under continuous monitoring (including intracranial pressure) and started treatment with acyclovir and antiplatelet and steroid therapy. At 12 h from admission, the patient developed raised intracranial pressure and anisocoria, which led to performance of a cranial CT scan. Based on the results of the scan, we decided to perform a decompressive craniectomy with placement of an EVD, which achieved stabilisation. The patient subsequently started rehabilitation and showed neurologic improvement, although sequelae were still present at the 4-month follow-up evaluation, including dysarthria, hypotonia, inability to stand and right hemiparesis. The follow-up cranial MRI scan revealed that the mass effect had resolved, but also significant cerebellar atrophy.

☆ Please cite this article as: Molina Corbacho M, Martín Birlanga F, Sarrion Sos N, Gargallo Tatay P, Tomás Vila M. Cerebelitis aguda fulminante, ¿una entidad infradiagnosticada?. *An Pediatr (Barc)*. 2019;90:188–190.