

- 2017;11, <http://dx.doi.org/10.1371/journal.pntd.0006062>, e0006062. PMID: 29099844; PMCID: PMC5687757.
2. Rana A, Mahajan SK, Sharma A, Sharma S, Verma BS, Sharma A. Neurological manifestations of scrub typhus in adults. *Trop Doct.* 2017;47:22–5, <http://dx.doi.org/10.1177/0049475516636543>. Epub 2016 Apr 7; PMID: 27059055.
 3. Biswas S, Ghosh R, Roy D, Ray A, De K, Biswas S, et al. Scrub typhus masquerading as limbic encephalitis. *Neurohospitalist.* 2022;12:105–10, <http://dx.doi.org/10.1177/19418744211016107>. Epub 2021 May 20; PMID: 34950396; PMCID: PMC8689554.
 4. Ghosh R, Biswas S, Mandal ADK, Bandyopadhyay S, Sardar SS, Mandal A, et al. Scrub typhus presenting as unilateral abducens nerve palsy. *Neuro-Ophthalmology.* 2021;29:1–5.
 5. Shen Y, Bao B, Cheng Z. Mild encephalitis/encephalopathy with reversible splenial lesion complicated with scrub typhus. *Neurol Sci.* 2018;39:1997–9, <http://dx.doi.org/10.1007/s10072-018-3510-3>. Epub 2018 Jul 27; PMID: 30054749.
 6. García-Monco JC, Cortina IE, Ferreira E, Martínez A, Ruiz L, Cabrera A, et al. Reversible splenial lesion syndrome (RESLES): what's in a name? *J Neuroimaging.* 2011;21:e1–14, <http://dx.doi.org/10.1111/j.1552-6569.2008.00279.x>. PMID: 18681931.
 7. Starkey J, Kobayashi N, Numaguchi Y, Moritani T. Cytotoxic lesions of the corpus callosum that show restricted diffusion: mechanisms, causes, and manifestations. *Radiographics.* 2017;37:562–76, <http://dx.doi.org/10.1148/rg.2017160085>. Epub 2017 Feb 6; PMID: 28165876.
 8. Mulroy E, Murphy S, Lynch T. Alexia without agraphia. *Ir Med J.* 2011;104:124. PMID: 21675099.
 9. Rodríguez-López C, Guerrero Molina MP, Martínez Salio A. Pure alexia: two cases and a new neuroanatomical classification. *J Neurol.* 2018;265:436–8, <http://dx.doi.org/10.1007/s00415-017-8691-9>. Epub 2017 Nov 27; PMID: 29181626.
 10. Mathew SSRPB. Alexia without agraphia-report of five cases and review of literature. *J Assoc Physicians India.* 2019;67:78–80. PMID: 31559778.
 11. Benito-León J, Sánchez-Suárez C, Díaz-Guzmán J, Martínez-Salio A. Pure alexia could not be a disconnection syndrome. *Neurology.* 1997;49:305–6, <http://dx.doi.org/10.1212/wnl.49.1.305>. PMID: 9222214.
 12. Damasio AR, Damasio H. The anatomic basis of pure alexia. *Neurology.* 1983;33:1573–83, <http://dx.doi.org/10.1212/wnl.33.12.1573>. PMID: 6685830.
 13. Stommel EW, Friedman RJ, Reeves AG. Alexia without agraphia associated with splenogenic-ulate infarction. *Neurology.* 1991;41:587–8, <http://dx.doi.org/10.1212/wnl.41.4.587>. PMID: 2011260.
 14. Greenblatt SH. Subangular alexia without agraphia or hemianopsia. *Brain Lang.* 1976;3:229–45, [http://dx.doi.org/10.1016/0093-934x\(76\)90019-5](http://dx.doi.org/10.1016/0093-934x(76)90019-5). PMID: 938929.
 15. Rupareliya C, Naqvi S, Hejazi S. Alexia without agraphia: a rare entity. *Cureus.* 2017;9:e1304, <http://dx.doi.org/10.7759/cureus.1304>. PMID: 28690938; PMCID: PMC5493472.
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- <https://doi.org/10.1016/j.nrl.2022.04.007>
 0213-4853/
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Acute inflammatory demyelinating polyneuropathy shortly after administration of intravitreal ranibizumab

Polineuropatía desmielinizante inflamatoria aguda tras la administración de ranibizumab intravítreo

Dear Editor:

Ranibizumab is a recombinant humanized IgG1 monoclonal antibody fragment that binds and inhibits vascular endothe-

lial growth factor (VEGF), an angiogenesis promoter.¹ Its use by intravitreal injection was initially approved by the Food and Drug Administration (FDA) in 2006 as a therapy for wet age-related macular degeneration (wet AMD) and has subsequently been approved in diabetic retinopathy and diabetic and ischemic macular oedema.² Its most frequently reported adverse effects (AE) are conjunctival hemorrhage, pain, decreased visual acuity, retinal detachment, and increased intraocular pressure.³ Anti-VEGF drugs have been associated with serious adverse reactions and systemic toxicity not only with systemic use but also with intravitreal administration. Recently an Italian study that analyzed a database of spontaneous reports⁴ identified 2472 cases of AE related to the use of these drugs in the areas of oncology and ophthalmology. However, systemic AEs were exceptional:



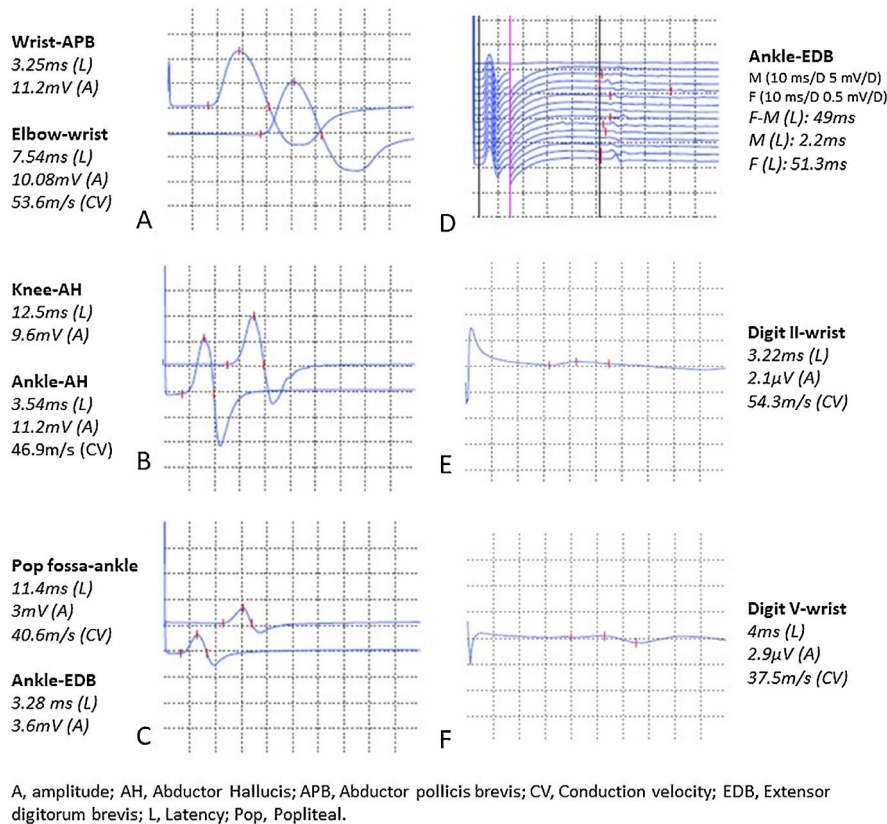


Fig. 1 Electroneurography performed four days from clinical onset. Electrophysiological examinations of the following motor nerves (scanning speed: 2 ms/D, sensitivity: 5 mV/D) are shown: right median nerve (A), left tibial nerve (B), and right peroneal nerve (C); with no remarkable findings. Right peroneal nerve F-waves showed increased latency (D). Electrophysiological examinations of sensory waves (scanning speed: 1 ms/D, sensitivity: 20 μ V/D): both superficial peroneal nerves sensory waves were absent (not shown). Right median nerve (E), left ulnar nerve (F) and right and left sural nerves sensory wave amplitudes were decreased. Left median nerve and right ulnar nerve sensory waves were not induced. These results fulfil the electrodiagnostic criteria for acute inflammatory demyelinating polyneuropathy.

single cases of cerebral hemorrhage, transient ischemic attack, and acute coronary syndrome. Additionally, other less severe and more frequent AEs related to parenteral administration have been described in the field of oncology such as hypertension and renal involvement.⁵ None of the currently available anti-VEGFs have been associated with dysimmune neuropathies such as AIDP (acute inflammatory demyelinating polyneuropathy). Nevertheless, cases have been described with other monoclonal antibodies such as Nivolumab,⁶ Ipilimumab,⁷ Pembrolizumab,⁸ Adalimumab.⁹ VEGF has been implicated in neuroregeneration functions in the Central and Peripheral Nervous Systems (CNS and PNS) stimulating remyelination in PNS through its effects on Schwann cells.¹⁰ It also promotes anatomic and functional recovery of injured peripheral nerves regardless of their angiogenic effects.¹¹

AIDP is an acute, often severe, fast-onset autoimmune polyradiculoneuropathy. Nowadays it represents the most common cause of acute or subacute generalized paralysis, having been compared in frequency with poliomyelitis.¹² We present the first report of AIDP after intravitreal injection of Ranibizumab.

Case report

50-Year-old-male patient, photographer, no family history of interest. Previous personal history of epilepsy in remission, treated with Carbamazepine and seizure free for more than 20 years. After experiencing deterioration of his visual acuity over two months he sought an ophthalmological consultation, and a diagnosis of wet AMD was made. Intravitreal Ranibizumab was administered in the left eye and oral ciprofloxacin was prescribed for five days as prophylaxis. After three days the patient developed tingling in the lower limbs, unsteadiness, and sinus tachycardia. He underwent an ENG (Fig. 1) that proved diagnostic of AIDP. All other ancillary tests were normal, including cerebrospinal fluid analysis, viral screen and antiganglioside antibodies. He underwent a 5-day cycle of intravenous immunoglobulins (0.4 mg $\times$ kg $\times$ day) with excellent clinical outcome and complete symptom resolution.

Discussion

Safety data reported in ophthalmology trials and pharmacokinetic and pharmacodynamic data provide strong

evidence that systemic events after intravitreal injection are very unlikely. A possible explanation could be found in the minimal dose used in ophthalmological disease (400 times less) and in the fact that the eye barrier implies a local sequestration of the drug and a delay in its systemic absorption. Nonetheless, it should be noted that this retinal blood barrier is altered in ophthalmological processes, and elimination is systemic even if the administration is local.¹³ Reported systemic AEs associated with this agent are related to toxicity on the vascular system. In addition, no cases of dysimmune diseases secondary to anti-VEGF have been described. Still, considering the neuromodulatory functions attributed to VEGF, these drugs could be a triggering factor in demyelinating diseases in some cases.

We describe a case of AIDP after use of intravitreal Ranibizumab. Our patient developed AIDP three days after treatment, with no history of infection or recent vaccinations. Other causal entities such as viral infections with *Campylobacter* Jejuni, Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and HIV were ruled out. There was also simultaneous use of ciprofloxacin, as fluoroquinolones (CF) have been exceptionally associated with AIDP.¹⁴ New users are at highest risk of developing CF-associated neuropathy¹⁵ but the patient does not remember if this was his first treatment.

Although this may be the first case of AIDP related to intravitreal Ranibizumab, we cannot establish a causal relationship because of confounding factors. Further clinical evidence is needed. Therefore, these conclusions should be interpreted with caution given the inherent limitations of spontaneously occurring AEs.

Disclosure

The author reports no funding or disclosures.

Authors' contribution

Drs. Fuerte-Hortigón, Sánchez-Sánchez and García-Campos, contributed equally to this work.

Bibliografía

- Blick SK, Keating GM, Wagstaff AJ. Ranibizumab. *Drugs*. 2007;67:1199–209, <http://dx.doi.org/10.2165/00003495-200767080-00007>.
- Lucentis (ranibizumab) FDA approval history – Drugs.com. (n.d.). Retrieved February 2021 from <https://www.drugs.com/history/lucentis.html>.
- Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration [published correction appears in *Ophthalmology*. 2013 Jan;120(1):209–10]. *Ophthalmology*. 2012;119:2537–48, <http://dx.doi.org/10.1016/j.ophtha.2012.09.006>.
- Cutroneo PM, Giardina C, Ientile V, Potenza S, Sottosanti L, Ferrajolo C, et al. Overview of the safety of anti-VEGF drugs: analysis of the italian spontaneous reporting system. *Drug Saf*. 2017;40:1131–40, <http://dx.doi.org/10.1007/s40264-017-0553-y>.
- Morales E, Moliz C, Gutierrez E. Renal damage associated to intravitreal administration of ranibizumab. Daño renal asociado a la administración intravítrea de ranibizumab. *Nefrología*. 2017;37:653–5, <http://dx.doi.org/10.1016/j.nefro.2016.10.011>.
- Supakornnumporn S, Katirji B. Guillain-Barré syndrome triggered by immune checkpoint inhibitors: a case report and literature review. *J Clin Neuromuscul Dis*. 2017;19:80–3, <http://dx.doi.org/10.1097/CND.0000000000000193>.
- Gaudy-Marqueste C, Monestier S, Franques J, Cantais E, Richard MA, Grob JJ. A severe case of ipilimumab-induced guillain-barré syndrome revealed by an occlusive enteric neuropathy: a differential diagnosis for ipilimumab-induced colitis. *J Immunother*. 2013;36:77–8.
- de Maleissye MF, Nicolas G, Saiag P. Pembrolizumab-induced demyelinating polyradiculoneuropathy. *N Engl J Med*. 2016;375:296–7, <http://dx.doi.org/10.1056/NEJMc1515584>.
- Manganelli S, Rossi M, Tuccori M, Galeazzi M. Guillain-Barré syndrome following adalimumab treatment. *Clin Exp Rheumatol*. 2012;30:592.
- Ruiz de Almodovar C, Lambrechts D, Mazzone M, Carmeliet P. Role and therapeutic potential of VEGF in the nervous system. *Physiol Rev*. 2009;89:607–48, <http://dx.doi.org/10.1152/physrev.00031.2008>.
- Pan Z, Fukuoka S, Karagianni N, Guaiquil VH, Rosenblatt ML. Vascular endothelial growth factor promotes anatomical and functional recovery of injured peripheral nerves in the avascular cornea. *FASEB J*. 2013;27:2756–67, <http://dx.doi.org/10.1096/fj.12-225185>.
- Ropper AH. The Guillain-Barré syndrome. *N Engl J Med*. 1992;326:1130–6, <http://dx.doi.org/10.1056/NEJM199204233261706>.
- Semeraro F, Morescalchi F, Parmeggiani F, Arcidiacono B, Costagliola C. Systemic adverse drug reactions secondary to anti-VEGF intravitreal injection in patients with neovascular age-related macular degeneration. *Curr Vasc Pharmacol*. 2011;9:629–46, <http://dx.doi.org/10.2174/157016111796642670>.
- Ali AK. Peripheral neuropathy and Guillain-Barré syndrome risks associated with exposure to systemic fluoroquinolones: a pharmacovigilance analysis. *Ann Epidemiol*. 2014;24:279–85, <http://dx.doi.org/10.1016/j.annepidem.2013.12.009>.
- Etminan M, Brophy JM, Samii A. Oral fluoroquinolone use and risk of peripheral neuropathy: a pharmacoepidemiologic study. *Neurology*. 2014;83:1261–3, <http://dx.doi.org/10.1212/WNL.0000000000000846>.

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<https://doi.org/10.1016/j.nrl.2022.04.005>
0213-4853/

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