

- .1007/s40618-015-0312-9. Epub 2015 Jun 11. PMID: 26062517; PMCID: PMC4630255.
3. Sindoni A, Rodolico C, Pappalardo MA, Portaro S, Benvenuto S. Hypothyroid myopathy: a peculiar clinical presentation of thyroid failure. Review of the literature. Rev Endocr Metab Disord. 2016;17:499–519, <http://dx.doi.org/10.1007/s11154-016-9357-0>. PMID: 27154040.
 4. Lee KW, Kim SH, Kim KJ, Kim SH, Kim HY, Kim BJ, et al. A rare manifestation of hypothyroid myopathy: Hoffmann's syndrome. Endocrinol Metab (Seoul). 2015;30:626–30, <http://dx.doi.org/10.3803/EM.2015.30.4.626>. Epub 2015 Sep 22. PMID: 26394732; PMCID: PMC4722421.
 5. Benito-León J, Martín E, Méndez M, Miguélez R, Luna E, Cabello A. Pseudohipertrofia muscular asociada a hipotiroidismo (síndrome de Hoffmann) [Muscle pseudohypertrophy associated with hypothyroidism (Hoffman's syndrome)]. Rev Neurol. 2001;32:998–9.
 6. Iughetti L, Vivi G, Balsamo A, Corrias A, Crinò A, Delvecchio M, et al. Thyroid function in patients with Prader-Willi syndrome: an Italian multicenter study of 339 patients. J Pediatric Endocrinol Metab. 2019;32:159–65.
 7. Butler MG, Theodoro M, Skouse JD. Thyroid function studies in Prader-Willi syndrome. Am J Med Genet A. 2007;143A:488–92, <http://dx.doi.org/10.1002/ajmg.a.31683>. PMID: 17304546; PMCID: PMC6706848.
 8. Reus L, Zwarts M, van Vlimmeren LA, Willemsen MA, Otten BJ, Nijhuis-van der Sanden MW. Motor problems in Prader-Willi syndrome: a systematic review on body composition and neuromuscular functioning. Neurosci Biobehav Rev. 2011;35:956–69.
 9. Udd B, Krahe R, Wallgren-Pettersson C, Falck B, Kalimo H. Proximal myotonic dystrophy – a family with autosomal dominant muscular dystrophy, cataracts, hearing loss and

hypogonadism: heterogeneity of proximal myotonic syndromes? Neuromuscul Disord. 1997;7:217–28, [http://dx.doi.org/10.1016/s0960-8966\(97\)00041-2](http://dx.doi.org/10.1016/s0960-8966(97)00041-2). PMID: 9196902.

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<https://doi.org/10.1016/j.nrl.2022.01.005>

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Terson syndrome as a marker of severity in acute brain injuries: More than meets the eye



El síndrome de terson como marcador de gravedad en las lesiones cerebrales agudas: más de lo que parec

Dear Editor,

Terson syndrome (TS) describes the presence of intraocular haemorrhage (pre-retinal, retinal, subhyaloid and vitreous) in patients with acute intracranial haemorrhagic pathologies. TS therefore features in a number of patients managed in the neurocritical care setting. Although TS can usually be managed conservatively and without significant long-term risks to vision, its presence can be suggestive of a more extensive neurological injury.^{1,2}

An interesting recent study from colleagues in Madrid confirms that a diagnosis of TS is associated with the most severe acute brain injuries including subarachnoid haemorrhage, traumatic brain injury and intracerebral haemorrhage.³ In a prospective study over 16 months, indirect ophthalmoscopy and ocular ultrasound were used effectively to diagnose TS, thus validating further these diagnostic techniques in TS. Further, TS was found to be an independent risk factor for in hospital mortality (odds ratio

4.15; 95% confidence interval 1.52–11.33).³ These findings are in keeping with previous publications demonstrating similar associations between TS, mortality and morbidity.⁴ Perhaps TS may find validation as a surrogate marker of the severity of its causative pathology – there may be more than meets the eye.

This paper is also important in that it highlights an increasing trend of the utilisation of ophthalmic testing in the neurocritical setting.⁵ Additionally, a greater role for ocular nerve sheath measurement, optical coherence tomography and similar testing can be expected for diagnostic and prognostic purposes. Equally, as contemporary CT and MRI scanning has sub-millimetre resolution, there may be a greater role for recognising TS in these modalities, given its prognostic importance.

All the same, an important question remains as to how TS is associated with poorer outcomes. Understanding the pathophysiological basis of TS is necessary. Previous theories included a sudden rise in intracranial pressure (ICP) transmitted to the optic nerve sheath leading to rupture of retinal vessels; or intracranial blood extending to the globe via the optic nerve sheath.^{1,6} The origin of blood in TS is not known for sure, but retinal vessels do not appear to be a likely source.⁷ In addition, an anatomical pathway for blood to enter the eye from the intracranial space had remained poorly defined.⁷

These concerns are mitigated in the glymphatic reflux theory of TS. The glial-lymphatic or glymphatic system is a recently discovered system of perivascular channels which

maintain flow of cerebrospinal fluid and interstitial fluid in the central nervous system – including the optic nerve and retina.⁸ The glymphatic system is the only defined extravascular pathway between the subarachnoid space and the retina. According to this theory, subarachnoid blood in the intracranial compartment refluxes into the globe when ICP exceeds intraocular pressure, resulting in intraocular haemorrhage.^{6,9}

The presence of TS may therefore be indicative of more widespread glymphatic dysfunction in more severe brain injuries. The glymphatic system is being appreciated as a major mediator of fluid transport and homeostasis in the brain under physiological circumstances.^{8,10} Conversely, glymphatic pathology is linked with cerebral oedema, hydrocephalus and inflammation.^{11,12} It is hereby hypothesised that worsening glymphatic dysfunction may link TS with severity in acute brain injuries.

Further studies may be necessary to determine if TS is indeed a surrogate marker of glymphatic damage. Advanced MRI techniques, including higher magnetic fields, have demonstrated perivascular glymphatic spaces in detail¹³ but remain as research methods only at present. Nonetheless, it is prudent to screen for TS in the most unwell patients, as it may guide management of patients' neurological injury. Dr Mesa Galán and colleagues are once again congratulated on an interesting and thought provoking study. Further studies are indicated.

References

- McCaron MO, Alberts MJ, McCarron P. A systematic review of Terson's syndrome: frequency and prognosis after subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry*. 2004;75:491–3, <http://dx.doi.org/10.1136/jnnp.2003.016816>. PMID: 14966173; PMCID: PMC1738971.
- Sung W, Arnaldo B, Sergio C, Juliana S, Michel F. Terson's syndrome as a prognostic factor for mortality of spontaneous subarachnoid haemorrhage. *Acta Ophthalmol*. 2011;89:544–7, <http://dx.doi.org/10.1111/j.1755-3768.2009.01735.x>. Epub 2009 Dec 9; PMID: 20003110.
- Mesa Galán F, Henríquez Recine LA, Robles Caballero MA, Yus Teruel A, García Martínez S, Egea-Guerrero JR, et al. Ultrasound diagnosis of Terson syndrome as an indicator of extreme severity in neurocritical care patients. *Neurologia (Engl Ed)*. 2022, <http://dx.doi.org/10.1016/j.nrleng.2020.04.026>. S2173-5808(22)00025-6. Epub ahead of print. PMID: 35305963.
- Czorlich P, Skevas C, Knospe V, Vettorazzi E, Richard G, Wagenfeld L, et al. Terson syndrome in subarachnoid hemorrhage, intracerebral hemorrhage, and traumatic brain injury. *Neurosurg Rev*. 2015;38:129–36.
- Sharma RA, Garza PS, Biousse V, Samuels OB, Newman NJ, Bruce BB. Ocular fundus abnormalities in acute subarachnoid hemorrhage: the FOTO-ICU study. *Neurosurgery*. 2021;88:278–84, <http://dx.doi.org/10.1093/neuros/nyaa411>. PMID: 32970100.
- Aboulhosn R, Raju B, Jumah F, Majmundar N, Prentner J, Matin T, et al. Terson's syndrome, the current concepts and management strategies: a review of literature. *Clin Neurol Neurosurg*. 2021;210:107008, <http://dx.doi.org/10.1016/j.clineuro.2021.107008>. Epub 2021 Oct 27; PMID: 34775364.
- Kumaria A, Gruener AM, Dow GR, Smith SJ, Macarthur DC, Ingale HA. An explanation for Terson syndrome at last: the glymphatic reflux theory. *J Neurol*. 2022;269:1264–71, <http://dx.doi.org/10.1007/s00415-021-10686-4>. Epub 2021 Jun 25. PMID: 34170402.
- Hablitz LM, Nedergaard M. The glymphatic system. *Curr Biol*. 2021;31:R1371–5, <http://dx.doi.org/10.1016/j.cub.2021.08.026>. PMID: 34699796.
- Kumaria A, Gruener AM, Lenthall RK, Ingale HA. Terson syndrome in reverse: intraventricular haemorrhage following primary intraocular haemorrhage. *Neurol Sci*. 2022, <http://dx.doi.org/10.1007/s10072-022-06053-4>. Epub ahead of print. PMID: 35384563.
- Rasmussen MK, Mestre H, Nedergaard M. Fluid transport in the brain. *Physiol Rev*. 2022;102:1025–151, <http://dx.doi.org/10.1152/physrev.00031.2020>. Epub 2021 May 5; PMID: 33949874; PMCID: PMC8897154.
- Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. *Lancet Neurol*. 2018;17:1016–24, [http://dx.doi.org/10.1016/S1474-4422\(18\)30318-1](http://dx.doi.org/10.1016/S1474-4422(18)30318-1). PMID: 30353860; PMCID: PMC6261373.
- Mogensen FL, Delle C, Nedergaard M. The glymphatic system (en)during inflammation. *Int J Mol Sci*. 2021;22:7491, <http://dx.doi.org/10.3390/ijms22147491>. PMID: 34299111; PMCID: PMC8305763.
- Eide PK, Pripp AH, Berge B, Hrubos-Strøm H, Ringstad G, Valnes LM. Altered glymphatic enhancement of cerebrospinal fluid tracer in individuals with chronic poor sleep quality. *J Cereb Blood Flow Metab*. 2022;29, <http://dx.doi.org/10.1177/0271678X221090747>, 271678X221090747. Epub ahead of print. PMID: 35350917.

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<https://doi.org/10.1016/j.nrl.2022.06.001>

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