

GUEST EDITORIAL

The scourge of ethambutol-related toxic optic neuropathy in the Philippines

It has been more than five years since the Philippine Journal of Ophthalmology devoted an entire issue on neuro-ophthalmology, a subspecialty that is still considered minor in terms of research and clinical practice, with less than 10 active practitioners locally.¹ That issue highlighted several neuro-ophthalmology papers submitted by local and international authors, as well as an editorial on optic neuritis and ethambutol-related toxic optic neuropathy (ETON). The following years saw members of the Neuro-ophthalmology Club of the Philippines (NOCP) focus on ETON in particular, a local “scourge” that is fraught with unique issues and controversies:

ETON not clearly addressed in the nationwide fight against tuberculosis

That we have a sound national TB program which has increased the country’s TB case-detection and treatment-success rates over the years is a given.^{2,3} What is particularly disturbing is that none of these programs clearly address the issue of ocular toxicity during treatment for TB. This should concern us. At the most modest estimate of 1% incidence of ETON in the foreign literature, we should be seeing at least 2,500 cases of ETON yearly based on our national TB incidence. With several studies showing a much higher incidence of ETON in those undergoing TB treatment, one can easily do the math as to the actual numbers of cases we should be seeing annually.^{4,5} In fact, we still do not have the actual incidence of ETON locally; neither do we have **official recommendatory guidelines** on monitoring the vision of these patients under TB treatment.

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A dearth of warning from prescribing physicians

Among local neuro-ophthalmologists with experience on ETON, the general consensus is that there is often a dearth of warning from prescribing physicians about the potential adverse ocular effects of anti-TB treatment. A local case series in 2005 of 19 patients diagnosed with ETON showed that 18 of these patients received NO warning at all from their prescribing physicians on the potential for visual impairment of anti-TB drugs.⁶ A random survey by Tamesis of 30 local physicians (internists, pulmonologists, family physicians) showed that while ALL 30 surveyed physicians followed the prescribed guidelines for TB treatment and were aware of ethambutol’s toxicity to the eye, not a single surveyed physician referred his patients to an ophthalmologist prior to treatment or warned them about the potential adverse ocular effects of TB treatment.⁷ Without a clear warning from the prescribing physician, the obvious consequences are delayed diagnosis and potential irreversible damage to the anterior visual system (as the patient continues the intake of ethambutol until a formal eye examination reveals the cause).

Another unfortunate consequence of this lack of warning is that it can lead to strained professional relationships, as the ophthalmologist is occasionally caught in the middle of 2 irate individuals: the patient (who is outraged by the lack of warning) and the prescribing physician (who may resent the ophthalmologist’s divulgence to the patient of the actual cause of his visual problems). It must be emphasized that part of our job is to protect the prescribing physician and avoid a potential medico-legal case.

More local studies needed

Few local studies on ETON have been published previously.⁸⁻¹¹

This issue of the PJO includes an excellent paper from Jose Reyes Memorial Medical Center.¹² The study looked at the incidence of color-vision abnormalities among patients enrolled in various DOTS (directly observed treatment short-course) centers in Metro Manila using

three different color vision tests: the Ishihara Pseudoisochromatic Plates, which is ubiquitous and is the color test of choice in terms of availability and ease of use for many local ophthalmologists, and the less commonly available Farnsworth Panel D-15 and Lanthony D-15 Desaturated tests. In this study, the Lanthony D-15 appears to be the most sensitive test in detecting early color-vision changes in ETON. This is consistent with other studies.¹³ Should we then discard the Ishihara Plates as our primary means to detect early ETON? Are these findings consistent for all cases and stages of ETON? Does it hold true even for severe cases of ETON? (which accounts for the majority of cases we see locally). We welcome more local studies like this looking into the clinical profile of local ETON cases. The insights we can glean from these local studies will definitely play an important role in any future efforts to come up with official recommendatory guidelines from the Department of Health (DOH) on the proper monitoring of Filipino patients undergoing TB treatment.

The Philippine National-Registry for Ethambutol-related Toxic Optic Neuropathy (PNR-ETON) Weblink Project

Over the past several years, the NOCP has taken the lead in raising awareness on ETON within the ophthalmic community. More importantly, this effort is being extended to our colleagues OUTSIDE the ophthalmic community, i.e., physicians who are actually prescribing these drugs. However, we cannot convince our colleagues without actual numbers. The PNR-ETON web site (<http://www.pnr-eton.com>), the first of its kind in the world, is a joint project of the NOCP, the Philippine Academy of Ophthalmology (PAO), and the Hope in Sight Foundation that aims to gather nationwide data on ETON. Hopefully, with enough local data at our disposal, we have better chances of convincing everyone else outside our profession about the dangers of ETON. Ultimately, these numbers will be the basis for any official recommendatory guidelines to be put out by the DOH and PAO in the future.

The PNR-ETON web site is basically a “primer” on ETON. Ophthalmologists are encouraged to visit the web site and learn more about this clinical condition (including background, presentation, diagnosis, monitoring, list of local studies, etc.) However, the main highlight of the web site is the actual REGISTRY. Ophthalmologists can report their cases via a one-page online form or download the form and submit it by fax or e-mail. At the very least, ophthalmologists can report

their cases via a short SMS to the NOCP. Clearly, we are trying to make it easy for our colleagues to submit their cases. Every Filipino EyeMD must realize that this responsibility falls upon our specialty “by default,” and that we cannot expect our non-ophthalmologist colleagues to do it for us because WE, not they, are the ones seeing the consequences of ETON. That many of them are not aware of the unfortunate visual outcomes in ETON cases can be traced back to us—because we are not reporting back what we see in our clinics. And if ophthalmologists will not take the lead in this effort locally, who else will?

The members of the NOCP hope to step-up their efforts along this project in the coming months through more lectures and workshops on ETON. The short-term goal is to gather ETON numbers locally, while the long-term goal is to effect policy changes in the national TB program based on the clinical insights we hope to glean from this registry. The NOCP cannot do this alone. We certainly need everybody’s help. It is our hope that together, our noble profession can one day overcome this local scourge that has caused considerable ocular morbidity in our populace.

References

1. Kho RC. The eye on neuro-ophthalmology. *Philipp J Ophthalmol* 2004; 29:158-159.
2. World Health Organization. Global tuberculosis control 2009: epidemiology, strategy, financing. 1st ed. Geneva: WHO Press; c2009. 137 p.
3. USAID: from the American people (Internet). Washington: United States Agency for International Development; 2009. Infectious diseases: Philippines; February 2009 (cited 2009 May 20). http://www.usaid.gov/our_work/global_health/id/tuberculosis/countries/asia/philippines_profile.html. Accessed December 1, 2009.
4. Choi SY, Hwang JM. Optic neuropathy associated with ethambutol in Koreans. *Korean J Ophthalmol* 1997; 11: 106-110.
5. Pyle MM. Ethambutol in the retreatment and primary treatment tuberculosis: a four-year clinical investigation. *Ann NY Acad Sci* 1966; 135: 835-845.
6. Kho RC. Ethambutol-related toxic optic neuropathy in the Philippines. Paper presented at: The Joint Meeting of the Philippine Academy of Ophthalmology and American Academy of Ophthalmology (PAO-AAO Joint Meeting); 2005 Nov 28 – Dec 1; Manila, Philippines.
7. Tamesis JM Jr, Cloma A, Bascara A. Ethambutol toxic optic neuropathy in the Philippines. *Neuro Ophthalmol Jpn* 2002; 19: 261-266.
8. Villanueva ME, Regner LV. Occurrence of vision problems among patients taking anti-tuberculosis medications. Paper presented at: Look the Future in the Eye. The Philippine Academy of Ophthalmology Annual Meeting; 2004 November 18-20; Manila, Philippines.
9. Bernardo EM 3rd, Cloma LAD, Uriate G, Tamesis JM Jr. Ethambutol toxic optic neuropathy: a patient demographic risk profile. Paper presented at: Look the Future in the Eye. The Philippine Academy of Ophthalmology Annual Meeting; 2004 November 18-20; Manila, Philippines.
10. Bernardo EM 3rd, Tamesis JM Jr, Cloma LAD, et al. Descriptive histopathologic animal study of ethambutol toxic optic neuropathy in the rat model. Paper presented at: Asian Neuro-ophthalmology Society-International Neuro-ophthalmology Society Joint Meeting; 2006 November 29-December 2; Tokyo, Japan.
11. Noche RR, Nicolas MG, Gonzaga NC. A study of the evolution of optic neuritis caused by ethambutol in rabbits. *Phil J Microbiol Infect Dis* 1987; 16: 42-46.
12. Cruz EM, Puentespina FG, Alejo KPL, et al. Color-vision abnormalities among patients undergoing tuberculosis treatment. *Philipp J Ophthalmol* 2010; 35: 3-9.
13. Chan RYC, Kwok AKH. Ocular toxicity of ethambutol. *Hong Kong Med J* 2006; 12: 56-60.

PHILIPPINE NATIONAL REGISTRY FOR EMB-RELATED TOXIC OPTIC NEUROPATHY

A. GENERAL INFORMATION

1. EyeMD/ REPORTER Information				2. PATIENT Information			
1a. Name				2a. Name			2b. Age
1b. Clinic Address				2c. Gender		2d. Ht	2e. Wt
				2f. City of Residence			
1c. Tel #		1d. Mobile #		2g. Contact #			
1e. Email				3. Date of Initial Consult (mm/dd/yy)			

B. HISTORY/SYMPATOMATOLOGY/DRUG INFO

4. Past Ocular Hx (List all previous Dx, if any)	4a. OD		4b. OS	
5. Systemic Disease (<i>special note</i> : inquire about kidney disease/status)				
6. Concomitant Drug Intake (other than anti-TB)				

7. Anti-TB REGIMEN 1: Brand Name (optional) _____ ; OR SPECIFY:

Component	Daily Dose in mg.	Start of Tx (mm/dd/yy)	End of Tx (mm/dd/yy)
Ethambutol (EMB)			
Isoniazid (INH)			
Rifampicin (RIF)			
Pyrazinamide (PZA)			
Px Compliance (check one)	GOOD	FAIR	POOR

8. Anti-TB REGIMEN 1: Brand Name (optional) _____ ; OR SPECIFY:

Component	Daily Dose in mg.	Start of Tx (mm/dd/yy)	End of Tx (mm/dd/yy)
Ethambutol (EMB)			
Isoniazid (INH)			
Rifampicin (RIF)			
Pyrazinamide (PZA)			
Px Compliance (check one)	GOOD	FAIR	POOR

9. Prescribing Individual's Medical Field/Specialty

10. Was the patient warned about potential adverse ocular effects of anti-TB drugs? (check one)	YES	NO	
11. How soon after intake of anti-TB meds did visual symptoms occur? (in weeks)			
12. Visual symptoms first noted in: (check one)	OD	OS	OU
13. FIRST visual parameter affected (check one)	Visual Acuity	COLOR	Others (specify)

C. EYE EXAMINATION

	OD	OS
14. Best Corrected Distance Visual Acuity on 1 st Consult		
15. Visual Field Defect (central, ceco-central , generalized, bitemporal, etc)		
16. Color Vision (Ishihara Color Plates)	___ out of ___	___ out of ___
17. Other Color Tests (please specify _____)		
18. Fundus Appearance (normal, optic disc pallor, cupping, retinopathy, etc)		
19. Concomitant Eye Disease/Diagnosis (cataract, glaucoma, etc.)		
20. Relative Afferent Pupillary Defect (RAPD)—leave blank if none		

Thank you for your contribution! Please submit the completed form by:
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