ETON

Background

Ethambutol Toxic Optic Neuropathy (ETON) is an emerging concern in countries that have a high prevalence rate of tuberculosis (TB) like the Philippines.[1]

Ethambutol hydrochloride (EMB) is a bacteriostatic, antimycobacterial drug, commonly used as part of the first-line quadruple therapy recommended by the World Health Organization in the treatment of Tuberculosis (TB) and is associated with Toxic Optic Neuropathy since its introduction in 1961. The exact mechanism of its toxicity is not known.

The onset of ocular toxicity is delayed and usually does not develop until after treatment for at least 1.5 months. Variable mean interval between onset of therapy and toxic effects have been reported from 3 to 5 months. It may manifest as late as one year after initiation of therapy.

Clinical Manifestations

- Bilateral blurring of vision (usually gradual but progressive worsening)
- Color vision abnormalities (specifically along the red-green hue)
- Visual Field Defects (Usually, Central/ Ceco-central Scotoma, Generalized Depression; less commonly, Peripheral Constriction, Bitemporal Hemianopia, Altitudinal Defects, etc.)
- Contrast abnormalities

(**Note**: Although visual damage is usually bilateral and symmetrical in nature for ETON, asymmetrical visual defects may be found in some cases. In addition, although there is clinical evidence of optic neuropathy, the fundus may appear grossly normal on direct examination)

Risk Factors

The safe clinical dosage of EMB as recommended by WHO for the treatment of tuberculosis is usually at 15 to 25 mg/kg/day.

- It has been postulated that incidence of EMB toxicity appears to be dose- and duration-

[1] The Philippines actually ranked ninth on the list classified by the World Health Organization (WHO) under "high TB-burden countries". In fact, the national statistics done by the Department of Health in 2010 claimed that over 90% of the population is exposed to TB. We have nearly a quarter of a million new TB cases each year, with an estimated incidence of 275/100,000 population and about 75 Filipinos die from TB daily. Thus, the occurrence of Ethambutol Toxic Optic Neuropathy is almost inevitable.

dependent.

- The incidence of ocular side-effects of EMB is reported in patients taking 60-100 mg/kg/day of the drug.
- 6% incidence at 25 mg/kg/day; rarely at 15 mg/kg/day
- No cases of ETON in 80 patients taking an average dose of 17 mg/kg/day for the duration of treatment
- No cases of ETON in13 patients taking an average dose of 16.2 mg/kg/day for the duration of treatment
- The average duration of EMB therapy before development of optic neuropathy was 235 days in postmarketing surveillance.

- The presence of co-morbidities may also be contributory
  - Pre-existing optic nerve damage like glaucoma were related to early occurrence of ETON
  - Advanced age & systemic diseases such as hypertension, diabetes and renal diseases were also associated with ETON

Diagnostic Tests

- Ophthalmological Evaluation
- Color vision testing prior to the start of Ethambutol therapy, and every month while patient is on medications[2]
  - Ishihara
  - Farnsworth Munsell D-15 (FD-15)
  - Lanthony and Hardy Rand & Ritler tests
- Visual Field Testing
  - ETON is often associated with central or ceco-central scotomas
  - Bitemporal hemianopias are also quite common which may reflect susceptibility to toxicity of chiasmal crossing fibers
  - Less commonly, bitemporal and altitudinal field defects also develop
- Neuroimaging is warranted since many conditions can mimic the clinical presentation of ETON---i.e., bilateral optic neuropathy that is progressive (secondary to inflammatory, ischemic, infiltrative, hereditary and compressive lesions).
- Optical Coherence Tomography (OCT) of the optic nerve and macula since thinning of retinal ganglion cell layer is a natural consequence of optic nerve damage. [3]

[2] In a study by Cruz et al., it was found out that the incidence of color-vision abnormalities among patients undergoing directly-observed treatment short course (DOTS) was 47.88% using the more sensitive color vision test, the FD-15 Lanthony Desaturated test after an average of 40 days on quadruple anti-TB therapy. The color-vision abnormalities returned to normal within an average of 38 days after discontinuing EMB.

Counseling & Management

- Educate patients on the possible ocular side-effects of EMB to the patient is really important
- They need to be referred back to their primary caregiver and meds must be stopped immediately if blurring of vision occurs.
- There is no standard treatment for ETON at present.
    - Vitamin supplementation was effective in reducing the risk and in reversing cases of color vision abnormalities among patients undergoing DOTS therapy for TB.
    - Another study found out that those given Zinc supplementation were minimally affected by the toxic doses of EMB as compared to those given EMB only wherein the retina, optic nerve and chiasm of animal subjects were markedly damaged.
    - Vitamin and Zn supplementation can also be given especially in those receiving higher doses of the drug, or in prolonged treatment due to advanced or resistant TB, to prevent ETON to occur.

Recommendations

- Ideally, all patients undergoing treatment for TB should have pre-treatment assessment of visual acuity (Snellen Chart) and color perception (Ishihara Color Plates and other color tests).
    - A formal ophthalmologic exam is still warranted to determine any pre-existing eye pathology (and perhaps also for medico-legal purposes).
- Advise the patient about the potential of anti-TB drugs to cause ocular toxicity.
    - Describe what symptoms to expect should this occur.
    - To guard against non-compliance of TB medication intake, explain that there is only a small risk of ETON occurring and that the condition should be detected early with proper monitoring.

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[3] In a study done by Delos Reyes et al., they found out that there's an initial increase in retinal nerve fiber layer (RNFL) thickness in patients starting anti-TB meds while chronic visual loss was associated with greater RNFL thinning if EMB treatment is prolonged. The results of this study suggest that OCT may be a useful ancillary procedure in detecting ETON. So, OCT could be included as part of the routine baseline and monthly evaluation to detect ETON before the onset of potentially irreversible visual symptoms.

    - Physicians must also be vigilant in detecting early the possible adverse effects of EMB in their patients especially with co-morbidities to avoid visual loss to happen.
- Monthly eye examinations should be performed from onset of treatment.
    - If it is impractical for the patient to visit the ophthalmologist monthly, the internist can become part of the monitoring process by checking BOTH visual acuity and color perception himself (if color tests are available in his clinic).
    - The internist can also do a monthly verbal query from the patient about possible evolution of visual disturbances.
    - Routine testing of visual acuity alone may be inadequate in early detection of ETON.
    - Other visual parameters like color perception may be affected earlier than visual acuity and should likewise be tested prior to treatment.
        - Dyschromatopsia in the form of red-green color deficiency may be the earliest sign of toxicity.
        - Blue-yellow wavelength may be more sensitive but it can only be detected by Desaturated Panel of Lanthony which it isn't readily available
        - For the ophthalmologist, other color tests (Farnsworth-Munsell 100-Hue test or Farnsworth D-15 Color Test) when available, may be utilized.
- Advise the patient to discontinue EMB from the anti-TB regimen when visual disturbances are experienced.
    - He should be seen by an ophthalmologist and assessed for ETON.
    - Once established as a diagnosis, the patient and prescribing internist must be advised about the possibility of permanently discontinuing EMB from the regimen.
    - If the toxic optic neuropathy is severe, it may be advisable to discontinue EMB together with the INH.
    - In less severe toxicity, INH may be continued, unless the optic neuropathy fails to stabilize six weeks after discontinuing EMB.
    - A formal neuro-ophthalmic work-up may be warranted to look for other causes of the patient's bilateral optic neuropathy.

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