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Thyroid peroxidase antibodies may induce demyelination and oculomotor neuromyotonia in the absence of thyroid eye disease

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Abstract

INTRODUCTION: The first report of oculomotor neuromyotonia (ONM) in a child induced by thyroid peroxidase antibodies (anti-TPO) in the absence of thyroid eye disease (TED).

CASE: 14-year-old girl complained of left eye (LE) paroxysmal upper lid fluttering and ptosis precipitated by hyperventilation or sustained left gaze. On sustained left gaze, right eye (RE) upper lid retraction and LE upper lid fluttering with ptosis ensued.

RESULTS: Diagnostic work-up revealed markedly elevated anti-TPO (> 600 IU/ml) and no TED. Brain MRI was normal with no signs of tortuous vessels presenting focal demyelination. We hypothesized that anti-TPO directly induced demyelination and set the ground for right ONM with ephaptic transmission between neurons supplying right medial rectus and levator muscle.

CONCLUSIONS: Plethora of theories try to decode the ONM. TED associated ONM is not reported in children but is the second most common cause of ONM in adults, advocated to be of compressive origin. Conversely, this case holds true for cross talk hypothesis. All extraocular muscles must be tested to determine the triggering one. ONM should not be overlooked due to its positive response to carbamazepine.

Abbreviations:

ONM	- oculomotor neuromyotonia	RE	- right eye
anti-TPO	- thyroid peroxidase antibodies	µg	- micrograms
TED	- thyroid eye disease	IU/ml	- international units per millilitre
LE	- left eye	mg	- milligrams

CASE REPORT

INTRODUCTION

Oculomotor neuromyotonia (ONM) is a rare clinical entity characterized by spontaneous, tonic, involuntary contractions of ocular muscles due to neural conduction abnormality of oculomotor, trochlear or abducens nerve, resulting in paroxysmal diplopia and strabismus (Yürüten & İlhan, 2003). ONM is characterized by episodic diplopia lasting seconds to minutes, usually provoked by prolonged eccentric gaze of the affected extraocular muscle (EOM) (Giardina *et al.* 2012; Yürüten & İlhan, 2003). Most cases are unilateral affecting adults (Giardina *et al.* 2012). Radiation therapy to the sellar and parasellar region appears to be the most common cause of ONM, followed by thyroid eye disease (TED) (Giardina *et al.* 2012; Yürüten & İlhan, 2003). Yet, systemic neuromyotonia in many cases seems to have autoimmune aetiology including diabetes, myasthenia gravis, hyperthyroidism, hypothyroidism, rheumatoid arthritis, coeliac disease and paraneoplastic processes (Giardina *et al.* 2012). Although neuromyotonia is a rare entity it is important to diagnose it due to its positive response to membrane-stabilizing agents that relieve the symptoms and signs of disease, advocating that unstable membranes of injured ocular motor axons may fire spontaneous impulses, resulting in involuntary and occasionally painful ocular muscle spasms (Stockman *et al.* 2018). Here we report for the first time a unique case of ONM in a 14-year-old girl induced by anti-thyroid peroxidase antibodies (anti-TPO) in the absence of TED.

CASE REPORT

A previously healthy 14-year-old girl, treated for hypothyroidism with levothyroxine 37.5 μg daily for a year, complained of episodes of paroxysmal left eye (LE) fluttering coupled with ptosis and upward eye deviation. Spontaneous episodes appeared during nights and were precipitated by hyperventilation that was waking her up and the spell accompanied with a headache ensued. The symptoms dissipated after several minutes. However, contractions could be triggered by voluntary prolonged left gaze, and the symptoms withdrawal elicited upon the left eye closure. Family history was positive for autoimmune thyroiditis: patient's mother and grandmother were diagnosed with autoimmune thyroiditis and older brother showed elevated levels of thyroid-stimulating hormone. The patient was referred to our Centre for ophthalmic examination.

Clinical examination revealed normal ductions and versions, yet the right eye (RE) abduction was painful. During sustained eccentric gaze depression, elevation, dextroversion, infradextroversion and supradextroversion were unremarkable. In infralevoversion, supralevoversion and levoversion, RE upper lid retraction and LE paroxysmal upper lid fluttering with ptosis were observed (Figure 1). While returning to primary position, the patient complained of pain, fatigue and dizziness. Otherwise the eye examination was unremarkable. Ultrasound B-scans excluded possible underlying orbital aetiology with symmetrical EOM thickness as measured by standardized A-echography.

A thorough diagnostic work-up and review of systems were unremarkable except markedly elevated anti-TPO count (> 600 IU/ml). No elevated acetylcholine receptor antibodies were reported. EEG and VEP were normal. Brain MRI was normal with no signs of tortuous vessels presenting focal demyelination. Thymoma and hypovitaminosis were ruled out.

Right third nerve ONM was diagnosed and oral carbamazepine 100 mg twice a day was introduced. The patient subjectively reported a decrease of spell frequency within a few days. After one month, on clinical examination, no signs of ONM were present.

DISCUSSION

Neuromyotonia belongs to the syndromes of sustained involuntary motor unit activity, still its precise pathophysiology is not yet clear (Giardina *et al.* 2012). The overlap between ocular and systemic neuromyotonia has yet to be decoded as anti-voltage gated potassium channel antibodies associated with systemic neuromyotonia were not identified in ONM (Stockman *et al.* 2018). It has long been suggested that ONM evolves in response to injury of both central and peripheral origin (Eggenberger, 1999). Anomalous conduction in peripheral nerves is debated to be due to ephaptic transmission or aberrant regeneration (Giardina *et al.* 2012). Ephaptic transmission most likely occurs as the result of demyelinated cell membranes (Giardina *et al.* 2012). Once the myelin sheath is damaged, axons may become susceptible to spontaneous firing. The cross talk facilitates that a single axon can excite neighbouring neurons, which in turn will reverberate the potential (Giardina *et al.* 2012; Stockman *et al.* 2018). Conversely, after denervation, reorganization of patterns of motor output in the nuclei and central neural disorganization by retrograde degeneration cause sustained muscle hyperactivity (Eggenberger, 1999).

Although in our patient the clinical hallmark was left upper lid ptosis and paroxysmal fluttering, the clinical pattern reflected right ONM. The spasm of the right medial rectus, elicited by sustained left gaze, initiated lateral interneural electrical transmission at the oculomotor nerve fascicle resulting in co-firing of neurons supplying right levator muscle. Superior right eyelid retraction with contralateral ptosis affirmed the lesion at the level of right oculomotor nerve fascicle. If central caudal nucleus is injured, the ptosis is bilateral, complete and symmetric. On the contrary, lesions of the nucleus of the posterior commissure, which send inhibitory fibers to the central caudal nucleus, result in disinhibition of the levator palpebrae muscle bilaterally and produce bilateral eyelid retraction (Kim *et al.*

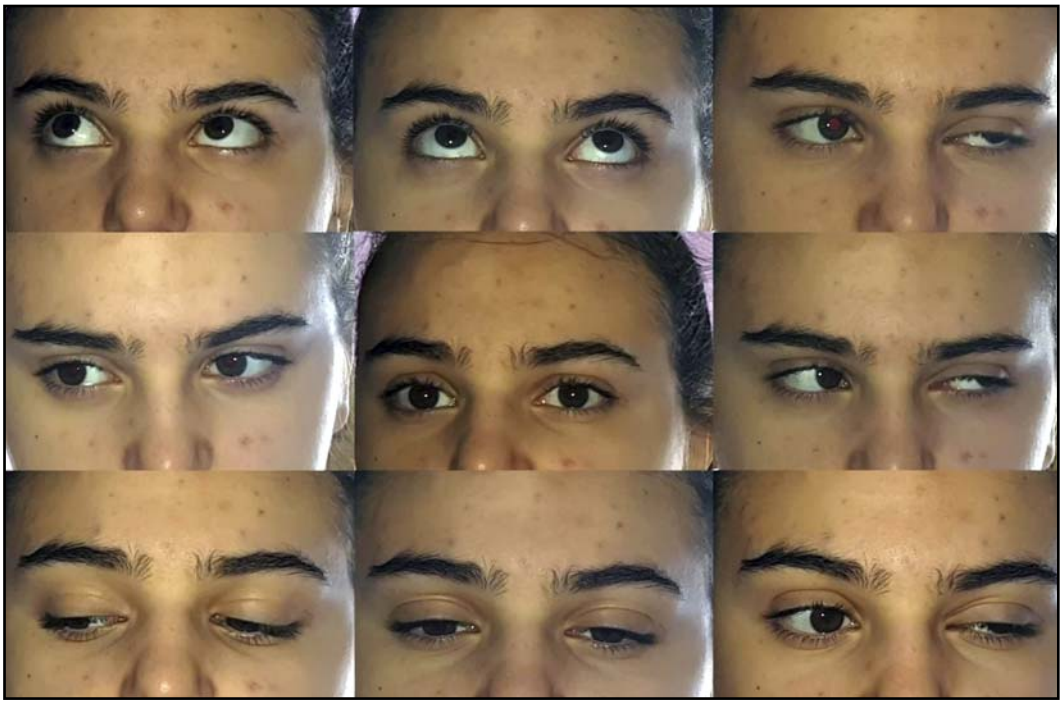

Fig. 1. Clinical examination. Depression, elevation, dextroversion, infradextroversion and supradextroversion were unremarkable, in infralevoversion, supralevoversion and levoversion, right eye upper lid retraction and left eye paroxysmal upper lid fluttering with ptosis were observed.

2013). Our patient presented with the third scenario, plus-minus syndrome (Kim *et al.* 2013). It could be that the fixating right eye's levator muscle needed less innate innervation due to the ephaptic transmission from medial rectus motor neuron, which in turn, according to Herring's law of equal innervation, resulted with contralateral ptosis. This phenomenon was revealed when the patient had closed the right eye, the ptosis was not noticeable. We hypothesized that spontaneous excessive medial rectus motor neuron firing was the result of demyelinated axons susceptible to spontaneous firing as the patient had significantly elevated titre of anti-TPO.

Careful examination should be undertaken to differentiate between ONM and SOM as these may be two entities within a spectrum of the same disease that have in common involuntary motor unit activity (Roper-Hall *et al.* 2013). In ONM there is a sustained tonic activity compared to SOM, attributed with phasic contraction and oscillopsia (Roper-Hall *et al.* 2013). Congenital oculomotor nerve paresis with ptosis, mydriasis, loss of accommodation and ophthalmoparesis are the characteristics of COPS (Giardina *et al.* 2012; Roper-Hall *et al.* 2013).

CONCLUSION

ONM associated with thyroid orbitopathy is advocated to be compressive in nature (Giardina *et al.* 2012). However, in our case, B-scan and standardized echography ruled out thyroid orbitopathy. As Giardina addressed, anti-TPO may trigger a cytokine or inflammatory cells release within the oculomotor muscles, and directly induce demyelination setting the ground for ephaptic transmission (Giardina *et al.* 2012). Supporting this hypothesis our patient had attacks of hyperventilation, that may expose the symptoms of demyelinating diseases (Tilikete *et al.* 2000). As in other ephaptic transmission events, carbamazepine was the treatment of choice (Stockman *et al.* 2018; Yürüten & İlhan, 2003). To the best of our knowledge, this is the first report of ONM associated with the high level of anti-TPO in the absence of TED. The case advocates for Giardina's theory that high levels of anti-TPO may cause demyelination enabling ephaptic transmission and ONM presentation. In the absence of a history of cranial irradiation, magnetic resonance imaging of brain and serum thyroid panel hormone with anti-TPO should always be investigated.

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