CASE REPORT

Meige Syndrome Secondary to Basal Ganglia Injury: A Potential Cause of Acute Respiratory Distress

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ABSTRACT: ***Background:*** Meige syndrome is a movement disorder that includes blepharospasm and oromandibular dystonias. Its etiology may be idiopathic (primary) or it may arise secondary to focal brain injury. Acute respiratory distress as a feature of such dystonias occurs infrequently. A review of the literature on Meige syndrome and the relationship between dystonias and respiratory compromise is presented. ***Methods:*** A 60-year-old woman suffered a cerebral anoxic event secondary to manual strangulation. She developed progressive blepharospasm combined with oromandibular and cervical dystonias. Neuroimaging demonstrated bilateral damage localized to the globus pallidus. Years later, she presented to the emergency department in intermittent respiratory distress associated with facial and cervical muscle spasms. ***Results:*** Increasing frequency and severity of the disorder was noted over years. The acute onset of respiratory involvement required intubation and eventual tracheotomy. A partial therapeutic benefit of tetrabenazine was demonstrated. ***Conclusion:*** This case highlights two interesting aspects of Meige's syndrome: (1) Focal bilateral basal ganglia lesions appear to be responsible for this patient's movement disorder which is consistent with relative overactivity of the direct pathway from striatum to globus pallidus internal and substantia nigra pars reticularis; (2) Respiratory involvement in a primarily craniofacial dystonia to the point of acute airway compromise.

RÉSUMÉ: Syndrome de Meige secondaire à une lésion du noyau lenticulaire, du noyau caudé, de l'avant-mur ou du noyau amygdalien comme cause potentielle de détresse respiratoire aiguë. ***Introduction:*** Le syndrome de Meige est un désordre du mouvement qui comporte un blépharospasme et de la dystonie oromandibulaire. Son étiologie peut être idiopathique (primaire) ou il peut survenir secondairement à une lésion cérébrale focale. La détresse respiratoire aiguë est une manifestation rare de ce type de dystonie. Nous présentons une revue de la littérature sur le syndrome de Meige et la relation entre les dystonies et l'atteinte de la fonction respiratoire. ***Méthodes:*** Une femme âgée de 60 ans a présenté un événement cérébral anoxique secondaire à une strangulation manuelle. Elle a développé un blépharospasme progressif associé à de la dystonie oromandibulaire et cervicale. La neuroimagerie a montré un dommage bilatéral au niveau du globus pallidus. Plusieurs années plus tard, elle s'est présentée à l'urgence en détresse respiratoire intermittente, avec des spasmes musculaires faciaux et cervicaux. ***Résultats:*** Une fréquence et une sévérité accrues de la symptomatologie ont été notées au cours des années. Le début brusque de la symptomatologie respiratoire a nécessité l'intubation et éventuellement la trachéotomie. Un bénéfice thérapeutique partiel a été obtenu avec la tétrabénazine. ***Conclusions:*** Ce cas illustre deux aspects intéressants du syndrome de Meige: (1) des lésions focales bilatérales du noyau lenticulaire, du noyau caudé, de l'avant-mur ou du noyau amygdalien semblent être responsables du désordre du mouvement chez cette patients, ce qui est en accord avec l'hyperactivité relative de la voie directe provenant du striatum vers le globus pallidus interne et la zone réticulée de la substance noire; (2) l'atteinte respiratoire allant jusqu'à l'obstruction aiguë des voies respiratoires chez un cas de dystonie crâniofaciale.

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Meige syndrome is a complex combination of cranial dystonias that may be primary or may arise secondary to brain injury. A case is presented of a woman with Meige syndrome that developed progressively following acute anoxic brain injury secondary to strangulation. The most interesting aspects of her case are that (1) neuroimaging provides evidence that her movement disorder is likely due to hypoxic injury to the globus pallidus bilaterally and (2) in addition to Meige syndrome, the musculature of the upper airway was also dystonic resulting in repeated episodes of acute respiratory distress. Using this example, the literature on the etiology, pathophysiology, presentation, and management of Meige syndrome will be reviewed. The involvement of the upper airway in cranial dystonias is also addressed.

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Case report

A 60-year-old woman (BH) presented to the emergency department with intermittent respiratory distress. Several episodes of acute difficulty breathing and severe respiratory distress were observed and coincided with spasmodic contraction of the facial and cervical musculature. This included severe and bilateral blepharospasm combined with complex oromandibular and cervical dystonias. The spasms were reduced with sedation. However, intubation was ultimately required to stabilize the airway.

On history, it was determined that this woman had suffered a diffuse anoxic injury to her brain six years earlier, likely secondary to strangulation. She was left with moderately impaired cognitive function, as well as poor short and long-term memory, but no apparent motor manifestations initially. Her movement disorder was first noted approximately two years later and began with mild blepharospasm. The symptomatology progressed over several years to include both oromandibular and cervical dystonias in addition to bilateral blepharospasm. The frequency and severity of this movement disorder steadily increased to the severe form present in the emergency department.

On examination she was observed to have intermittent spasms of her bulbar musculature, including:

(1) severe bilateral blepharospasm with the eyes firmly closing and only opening again once a spasm had subsided. The force of closure would vary with spasmodic activity of the obicularis oculi observable while the eyelids remained shut. Manual retraction of the lids failed to reveal more than 10% of the globes;
(2) complex oromandibular dystonias where the musculature of the mouth was observed to open, close and separate the lips in an asymmetric and variable pattern. Involvement of the tongue was also noted with occasional protrusion from the mouth;
(3) cervical dystonias that were also asymmetric and variable and included torticollis as well as ante-, retro-, and latero-collis.

The severity of respiratory distress and dystonia were well correlated. During severe muscle spasm, evidence of respiratory distress including intercostal indrawing, accessory muscle use, and intermittent perioral cyanosis were observed. There were numerous choking sounds and movements, however no audible stridor was heard. No paradoxical breathing was noted. Several acute drops in O_2 saturation were recorded, with values as low as 70%, that improved only slightly with oxygen administration. These episodes lasted from 30 seconds to several minutes. Resolution was spontaneous with saturations returning to above 90% concomitant with decrease in muscle dystonias. Respiratory compromise did not recur following endotracheal intubation, despite ongoing craniofacial dystonia.

Following admission to hospital, the dystonic episodes were observed to last anywhere from 10 seconds to several minutes, occurred throughout the day and ceased during sleep. Between spasms, cranial nerve examination was unremarkable, with normal corneal, jaw jerk and gag reflexes. Motor exam was abnormal only in gait, which was mildly slowed and wide based. Cerebellar testing demonstrated both dysmetria and dysdiadokokinesia. Reflexes and sensory examinations were normal. The remainder of the physical exam was normal except for depigmentation of the hands bilaterally, consistent with vitiligo.

CT scans, completed on the day of injury and three days later, demonstrated evolving damage consistent with ischemic injury to multiple areas, including bilateral medial temporal lobes, cerebellum and basal ganglia, most notably the globus pallidus (see Figure).

Discussion

Meige syndrome

Meige syndrome is classically defined as the combination of blepharospasm and oromandibular dystonia. The prevalence rate of cranial dystonias in general has been estimated at 5-10 per 100,000[1] and Meige syndrome is a relatively common example with one of its components, isolated blepharospam, being the most common. It has also been called blepharospasm-oromandibular dystonia,[2] blepharospasm-orofaciocervical dystonia syndrome,[3] and idiopathic orofacial dystonia.[4] It has also been used synonymously with Brueghel's syndrome, although recent reports suggest this disorder is distinct from Meige syndrome in that it includes wide opening of the jaw, paroxysmal hyperpnea and an upbeating nystagmus that suggests a pontine localization.[5] Meige syndrome was first described by the French neurologist Henry Meige, in 1910, as *spasme facial median*. He noted the association of prominent blepharospasm with oromandibular dystonia, described the involvement of the cervical musculature, and even postulated lesions of the mesencephalon as the underlying cause.[6] Poorly established risk factors for developing Meige syndrome may include a family history with some evidence for an autosomal dominant pattern of inheritance[3,7-9] or history of immune mediated disorders such as rheumatoid arthritis, Sjogren's syndrome, thyroid disorders, or myasthenia.[3] Although associated with these autoimmune disorders, a relationship between vitiligo and Meige syndrome, both apparent in this case of presumably secondary Meige syndrome, has not been reported. The majority of cases of this movement disorder are reported to be idiopathic and are therefore deemed primary. However, secondary Meige syndrome has been suggested to occur following several neural insults including focal brain injury as may be the case here and will be discussed below.

Primary Meige syndrome

The clinical manifestations of primary Meige syndrome are relatively uniform and include spasmodic contraction of the orbicularis oculi (blepharospasm) combined with contractions of the middle and lower facial musculature. Less commonly, these two features may occur independently and are referred to as "essential blepharospasm" and "oromandibular dystonia syndrome" respectively.[9] Peak onset is reported to occur in the sixth decade and women are affected more often than men.[2,10] Blepharospasm may take the form of sustained tonic muscle dystonia or brief, repetitive clonic contractions (blepharoclonus) or some combination of both. While up to 25% of cases may begin with unilateral eye involvement, almost all will progress to bilateral involvement although it may remain asymmetrical.[11] Also, many patients may experience difficulty in opening their eyes following an episode of blepharospasm, even though the contraction of orbicularis oculi has apparently ceased.[9] This feature was particularly noticeable in this case and appeared to closely resemble an "apraxia of lid opening".[12] While this did not represent a true apraxia of lid opening, such mimicking has been previously described.[13] Furthermore, while Meige syndrome patients are often seen to use "tricks" to re-open their eyes in such circumstances, this particular patient was never observed to do so. Such maneuvers have been reported to include extending

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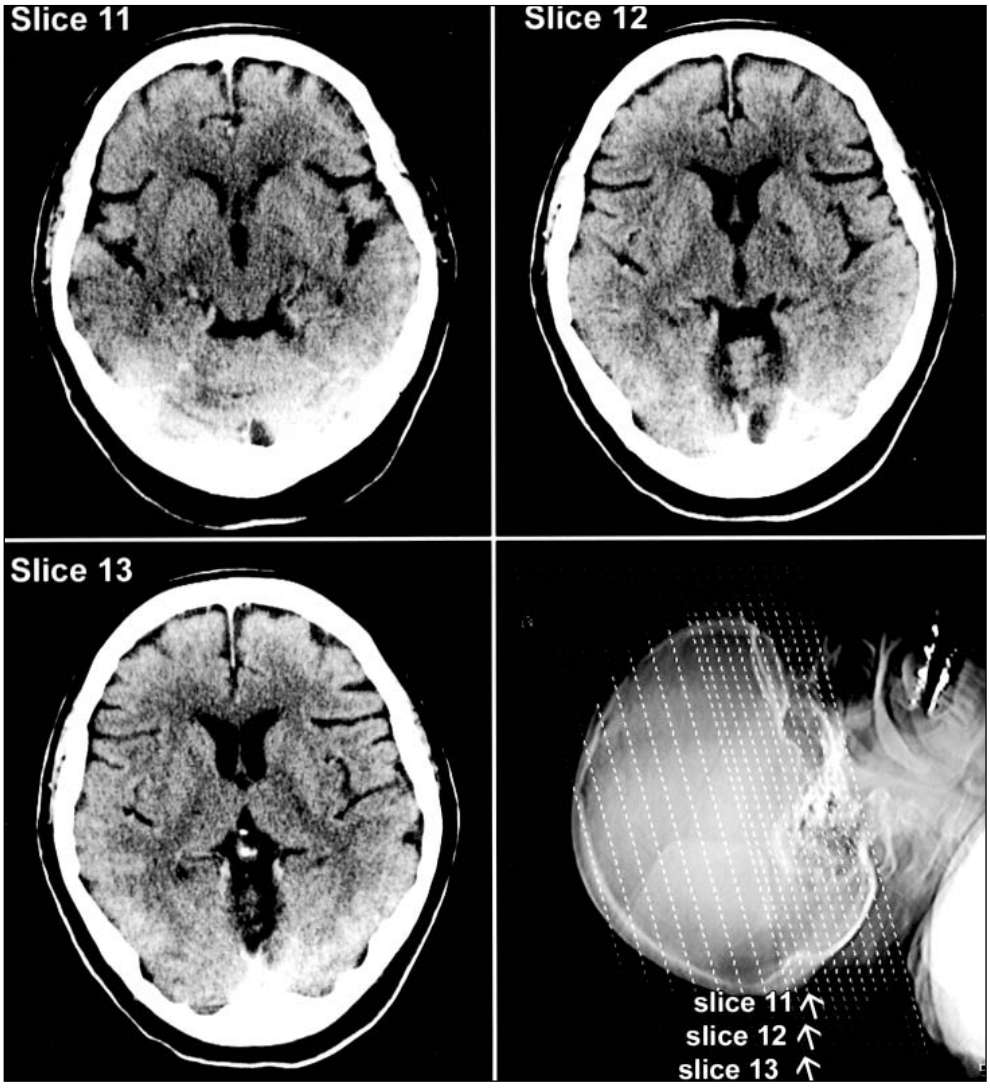

Figure: *Sequential computerized tomographic slices through the basal ganglia of patient B.H. The scan was carried out three days following the initial acute insult. Multiple areas of hypodensity in deep ganglionic structures are seen in Slice 11 (bilateral), Slice 12 (left), and Slice 13 (right).*

the head or manually opening the eyes with their hands.[3] However, in the case of BH, if an observer to an episode of spasm was to mechanically lift her lids open with their fingers, the eyes would immediately open and remain so until the next blepharospasm occurred.

Involvement of the middle and lower facial musculature in primary Meige syndrome is variable and has been reported to include lip pursing, platysmal contraction, jaw opening and closure, nasalis contractions and tongue protrusion.[9] Involvement of laryngeal, pharyngeal and even respiratory musculature is discussed below. Other extracranial involvement is commonly reported in association with Meige syndrome, although the form and frequency appear highly variable.[2,3,4] These often include cervical dystonias[3] which may assume the form of cervical movements in a single plain or may be more complex combinations of torti-, ante-, retro-, and latero-collis as were observed here.

Numerous aggravating and relieving factors have been identified in Meige syndrome. Worsening of spasms may occur with bright lights, watching television, certain directions of gaze, reading, walking or general stress. Asking a patient to repetitively open and close their eyes at a frequency of once per second has been reported to stimulate blepharospasm.[9,15] No specific aggravating factors were identified in this case. Sleep has been suggested to both worsen and relieve spasms in Meige syndrome, while in this case no spasms were observed during sleep. Maneuvers reported to alleviate Meige-type dystonias include talking, singing, chewing, blowing air out of the mouth, yawning, lying down, or "touching the eyebrows or side of the face".[9,16,17] This last technique, a so-called *geste antagoniste*, is of interest in that the patient did appear to use a similar "trick" in an attempt to minimize the severity and/or frequency of her spasms. This usually took the form of light stroking of her chin, cheeks and forehead with the index finger of either hand. When

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questioned, she reported that this helped decrease her spasms. During her stay in hospital, the patient was seen to execute variations of this behaviour nearly constantly while awake.

It should be noted here that many of the features associated with primary Meige syndrome were observed in this patient who presumably has a secondary Meige syndrome. This might imply similarities in the pathophysiology of the two conditions, whereby alterations at certain anatomical or biochemical locations are occurring in both, with the only difference being an identifiable precipitant in secondary Meige syndrome.

Secondary Meige syndrome

Numerous etiologies for secondary Meige syndrome have been suggested. The most common is chronic neuroleptic medication (tardive dystonia syndrome) but also included are other drug-induced causes such as chronic levodopa therapy in Parkinson's disease, and more rarely, chronic use of amphetamines, antihistamines or anticholinergics.[18,19] Of more interest here is whether focal brain injury or pathology, such as that suffered by this patient, can account for the development of Meige syndrome. Numerous associations with organic brain disease have been noted including kernicterus, progressive supranuclear palsy (PSP), Tourette's syndrome, Huntington's disease, Parkinson's disease, Wilson's disease and numerous inborn errors of metabolism.[9,20] Debate over localization of the primary area of injury leading to Meige syndrome has been divided; however, the basal ganglia have been a popular location for theories to explain both Meige syndrome and other forms of dystonia.

Pathophysiology

A role for involvement of the basal ganglia in Meige syndrome is supported by the noted association of similar dystonias in neurological disorders involving these regions of the brain. This would include Parkinson's, Huntington's and Wilson's diseases as well as PSP, regional ischemic infarction and neuroleptic or dopaminergic drug-induced dystonias. Blepharospasm following anoxic encephalopathy[21] and bilateral basal ganglia infarction[22] has been reported and, given the relative sensitivity of the basal ganglia to hypoxic injury, such an association is not surprising. Several studies support a role for the contralateral basal ganglia in producing focal hemidystonia.[23-25] A role for basal ganglia damage in primary Meige syndrome, as well as alterations in dopaminergic neurotransmission, is supported by recent evidence that D_2-like binding of dopamine is impaired in the putamen of patients with idiopathic focal dystonias including blepharospasm and oromandibular dystonias.[26] Putamenal lesions have been identified by imaging studies in patients with presumed secondary dystonias.[27-30] While these studies focus on the putamen, involvement of the entire lentiform nucleus has also been associated with cervical dystonias,[31] although more selective damage to the putamen has also produced such dystonia.[32] Therefore, this case is of particular interest in that the imaging studies completed to date suggest relatively focal damage to the globus pallidus with potential sparing of the putamen in someone with Meige syndrome.

A recent review on the pathophysiology of dystonia[33] suggests that abnormalities at all levels of the neuraxis – from muscle to spinal and brain stem reflexes to sensory processing to extrapyramidal function to sensorimotor cortex – have been identified in dystonia patients. However, the most convincing evidence points to the basal ganglia, specifically striatal control of the internal segment of the globus pallidus (GPi) and substantia nigra pars reticularis (SNr), the convergence elements of the direct and indirect pathways. The primary outflow from these sites is an inhibitory influence on motor centers in the thalamus which in turn exhibit an excitatory effect on prefrontal and sensorimotor areas of cortex responsible for motor planning and execution of movement. One proposed model suggests that this may then result in abnormal control of brain stem and spinal cord interneuronal inhibitory mechanisms that ultimately lead to dystonia.[33] Decreased mean discharge rates in the GPi are strongly associated with the involuntary movements of hyperkinetic movement disorders.[34] Alterations in activity of both the direct and indirect pathways (which additionally involves the external segment of globus pallidus (GP) and the subthalamic motor nucleus) may be involved in the development of dystonias.[34] Rather than a simple loss of function, some combination of altered discharge patterns, synchronization, or response to sensory input of crucial areas in the GP are likely involved in the development of hyperkinetic movement disorders. It is reasonable to suspect that the hypoxic injury suffered by this patient, involving both areas of the GP, may well have produced such alterations that lead to her Meige syndrome. In keeping with this theory, internal segment pallidotomy, recently demonstrated to improve generalized dystonias,[34] might provide an alternative to medical management.

In addition to anatomical localization, the neuropharmacology of dystonias also provides important clues about the mechanisms of Meige syndrome. Cranial dystonia has been correlated with increased dopamine levels in the red nucleus and increased norepinephrine (NE) levels in the red nucleus and substantia nigra.[35] This study also demonstrated altered NE levels in the GPi. Other studies have suggested striatal dopaminergic preponderance,[10] dopamine receptor hypersensitivity[36] or impaired binding of dopamine,[25] and excess cholinergic activity.[37] Both antidopaminergic and anticholinergic medications have been reported to alleviate cranial dystonias[36] with some evidence that the latter is more effective.[38] Cholinesterase inhibition with physostigmine worsens such movement disorders and has been proposed as a pharmacological means to differentiate tardive dyskinesia from cranial dystonia.[37] The inconsistency of therapeutic interventions is a testament to the complexity and relatively poor understanding of the neurotransmitters involved in Meige syndrome and similar syndromes.

As opposed to the basal ganglia being the primary site for an Meige syndrome-inducing lesion, Meige himself originally predicted a mesencephalic localization of the movement disorder that now bears his name.[6] Upper brain stem diencepahlic lesions secondary to strokes and demyelinating lesions have been described in Meige syndrome patients.[17] Further associations between blepharospasm and diencephalic damage secondary to ischemia, head trauma, normal pressure hydrocephalus, olivopontocerebellar atrophy, bilateral thalamectomy and mass lesions have been reported.[39,40,41] In addition, focal brain stem lesions in the region just above the pontine facial nucleus have

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been observed to cause orofacial dystonias and blepharospasm.[9] Finally, inclusion of mesencephalic structures in the indirect pathway mentioned above, such as the subthalamic motor nucleus, may also be consistent with lesions in this region promoting the development of a dystonia.

Therefore, evidence exists for involvement of both basal ganglia and brain stem structures in the pathogenesis of Meige syndrome. While a detailed discussion of the underlying pathophysiology is beyond the scope of this review, it is possible that a contribution from both of these anatomical divisions may be responsible. A study focusing on the role of facial reflexes in blepharospasm and oromandibular dystonia concluded that the neuronal arcs of these reflexes were normal. However, the evidence provided suggests that an abnormal excitatory drive, possibly from dysfunctioning basal ganglia, may alter the motor and interneurons that mediate these brain stem reflexes to produce the features of Meige syndrome.[33]

Finally, the time between the initial hypoxic-ichemic injury and the development of secondary Meige syndrome was a particularly interesting feature of this case. Such a delay has been reported to vary from several days to several years with the initial and predominant symptom being blepharospasm.[17] This patient's symptoms appeared at least two years following her initial brain injury, beginning with blepharospasm, and have steadily evolved to the present. The underlying mechanism for this temporal evolution may involve a degree of functional reorganization (plasticity) with time-dependent changes occurring in the basal ganglia following the initial injury. Such plasticity and its role in movement disorder has been described in other conditions following brain injury of various etiologies.[42,43] This includes numerous animal studies demonstrating functional re-organization of striatal neurochemistry following hypoxic-ischemic injury to the developing brain.[44-46] More specifically, the selective recovery of D_1 over D_2 receptor populations following such injury has been postulated to produce a lasting imbalance in neostriatal output pathways, affecting the indirect pathway relative to the direct.[47]

Treatment

No definitive medical treatment has been identified for Meige syndrome, although variable responses have been noted to numerous agents. These include tetrabenazine, several anticholinergics, baclofen, pimozide and clonazepam.[9] A role for melatonin has also been proposed.[15] Long-term control with oral medications is only achieved in approximately 25% of cases.[3] Regional injections of botulinum toxin have provided dramatic symptomatic relief, particularly of blepharospasm where success is estimated at 85-90% but usually needs to be repeated every three to four months.[16] This form of treatment is more difficult to apply to other cranial and extracranial musculature and the long term effectiveness has not been established. Three surgical options of variable success include avulsion of facial nerve fibers, orbicularis oculi stripping and percutaneous thermolysis of facial nerve branches.[16] This patient did appear to respond transiently to sedation with benzodiazepines. Tetrabenazine treatment has been successful in reducing both the frequency and intensity of her spasms, although high doses (50 mg tid) were required and the long-term efficacy remains to be determined.

Outcome

The clinical course and prognosis of primary Meige syndrome is variable. Spontaneous remissions do occur but are rare and likely constitute only about 1% of cases.[11] Chronic progression, usually over a period of weeks to months to reach maximum, is the most common pattern. This particular case appears to have developed more slowly, at present still worsening after approximately four years of symptoms. Progression to only mild blepharospasm with minimal or no disability, may occur in approximately 15-35% of cases.[8,14] Further progression will often lead to difficulties with activities of daily living such as reading and driving as well as social embarrassment. As many as 35% will progress to severe Meige syndrome where eye closure is so prolonged and frequent that the patient is rendered functionally blind.[9,14] Chronic and recurrent conjunctivitis and/or blepharitis often complicates Meige syndrome, particularly in the severe form, and was noted to have occurred at least a dozen times in this person.

Airway obstruction and dystonia

Clinically, this patient demonstrated severe respiratory distress in association with her dystonias. The most convincing evidence for upper airway involvement was that all respiratory compromise resolved following tracheotomy, despite the continuation of facial and cervical dystonias. As mentioned, cranial dystonias are often reported to involve all varieties of musculature innervated by the cranial nerves and possibly others that are not. This may include both laryngeal as well as respiratory musculature. Extensive review of the literature reveals no specific case reports of patients with Meige syndrome experiencing such severe respiratory compromise as part of their movement disorder. The question raised is whether the respiratory component is a result of laryngeal muscle dystonia that is creating an upper airway obstruction or whether the respiratory muscles themselves may be involved.

Upper airway obstruction in cranial dystonia

Various disturbances of laryngeal function may subsequently lead to respiratory dysfunction, possibly via inappropriate approximation of the true or false vocal cords.[48] Normal respirations and phonation require intricate coordination of laryngeal and pharyngeal musculature. Normal swallowing involves a coordinated reflex that includes closure of the glottis. Difficulty swallowing has also been associated with Meige syndrome and other cranial dystonias.[48] In addition to several case reports suggesting an association of dysphagia and Meige syndrome,[2,49,50] another study confirmed disordered spasmodic contraction of deglutition muscles by EMG in a patient with Meige syndrome and coinciding spasmodic dysphagia.[51]

Spasms of laryngeal muscles in Meige syndrome or other focal cranial dystonias have been suggested previously[52] but not confirmed experimentally. Furthermore, there is little or no reported evidence of such laryngeal involvement inducing the degree of respiratory compromise observed in this case. Laryngeal involvement in Meige syndrome is also suggested by associated "spasmodic dysphonia", defined as a change in the pitch or tone of a patient's voice during spasmodic contractions of other cranial musculature. This is reported to occur in as many

as 20% of patients with Meige syndrome.[3] Spastic dysphonia is a clinically recognized, albeit uncommon, speech disorder that may involve the hyperadduction of the true and false vocal cords. The cause of this disorder is poorly understood although damage to extrapyramidal systems has been suggested.[53] It can occur in isolation or as part of another movement disorder such as Tourette's syndrome, torsion dystonia, or spasmodic torticollis.[54] Despite the specific involvement of laryngeal musculature with forceful closure as a result of dystonia occurring in spasmodic dysphonia, no association with acute respiratory compromise has been reported. This may suggest that, although the laryngeal muscle tone may be altered by focal dystonias, the degree is seldom severe enough to create actual airway obstruction. Laryngeal stridor has been associated with focal dystonia. Gerhardt's syndrome is laryngeal stridor caused by narrowing of the glottic aperture due to paralysis of vocal cord abductors bilaterally.[53] As opposed to spastic dysphonia, this disorder is not only apparent with phonation and often assumes the form of chronic, intermittent stridor. A small study that included some patients with multifocal dystonias demonstrated electrophysiologically that at least some cases of apparent Gerhardt's syndrome are in fact due to focal dystonia of laryngeal adductors rather than paralysis of corresponding abductors.[55]

Respiratory system and dystonia

Respiratory involvement in dystonias appears to be uncommon. However, such involvement may be inconspicuous and the frequency may be underestimated.[56] As many as 15% of patients with tardive dystonias have clinically demonstrated respiratory involvement such as grunting or irregular respiratory patterns. Interestingly, the vast majority of these patients also demonstrate cranial dystonias.[57] A small case series of patients with adult-onset dystonias with respiratory involvement demonstrated convincing correlation between clinical signs of respiratory compromise such as deep inspirations or breathing arrests with electrophysiologic evidence (EMG) of impairment of the respiratory musculature including the diaphragm.[56] Therefore, although uncommon, extension of cranial dystonias to involve the respiratory muscles directly does appear to occur and may account for, or in part contribute to, respiratory compromise during active muscle spasms in conditions such as Meige syndrome.

In conclusion, this case highlights several unique issues in a patient with Meige syndrome. Firstly, the delayed development of the syndrome secondary to bilateral basal ganglia injury, specifically the globus pallidus, that was in itself induced by strangulation-induced cerebral hypoxia. Secondly, the presentation of this movement disorder in the form of acute respiratory distress, likely secondary to upper airway obstruction, requiring intubation and tracheotomy. This case highlights some of the diversity in etiology, presentation and management issues of this fascinating movement disorder.

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