WEBINO and the Return of the King's Speech

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A 69 year-old man with hypertension who developed the sudden onset of horizontal binocular diplopia and stuttering of speech. On examination, bilateral exotropia (i.e. 'wall-eyed') was observed in the primary position. Attempted horizontal saccades revealed bilateral internuclear ophthalmoplegia; all consistent with the wall-eyed bilateral internuclear ophthalmoplegia (WEBINO) syndrome. Convergence, vertical saccades and vestibular ocular reflexes were likewise impaired. Pupillary and levator palpebrae superioris functions were intact. Mild left-sided dysmetria, intention tremor and dysdiadochokinesia were elicited. Conspicuously, further characterization of the patient's history revealed that he had stuttered as a child, but it had resolved in adolescence. Brain MRI revealed an acute infarction of the mesencephalic and upper pontine tegmentum involving the periaqueductal gray region and the medial longitudinal fasciculus bilaterally with greater involvement of the left. Like the WEBINO syndrome, re-emergent developmental stuttering is a rare neurologic phenomenon. To our knowledge, this is the first case report of a mesencephalic and upper pontine infarction causing both syndromes. We discuss the pathobiological underpinnings of the WEBINO syndrome and neurogenic stuttering and in relationship to this unusual case.

1. Introduction

1.1. Case report

A 69 year-old man with hypertension presented to the emergency department with acute horizontal diplopia and dysfluency. Bilateral exotropia (i.e. 'wall-eyed') was observed in the primary position. Attempted horizontal saccades revealed bilateral internuclear ophthalmoplegia (INO). Convergence, vertical saccades and vestibular ocular reflexes were likewise impaired. This picture was characteristic of the wall-eyed bilateral internuclear ophthalmoplegia (WEBINO) syndrome. Alternately, pupillary and levator palpebrae superioris functions were intact. Subtle left-sided dysmetria, intention tremor and dysdiadochokinesia were elicited. Spontaneous speech, reading and repetition was slow and halting albeit grammatically intact with frequent repetitions, hesitations and blocks of initial syllables. This persisted during recitation of familiar nursery rhymes and singing well-known songs (e.g. Happy Birthday). There was no improvement with repeated reading of the same text. No facial grimacing, fist clenching, head jerks, or other accessory behaviors were observed. Although annoyed by his dysfluency, he was not overly anxious. Comprehension, naming, writing and calculation were intact. Conspicuously, the patient stuttered as a child, but it had resolved in adolescence. Brain MRI revealed an acute midbrain infarction, extending from the periaqueductal gray (PAG) region to the interpeduncular fossa. Also involved in the midbrain was the area where the fibers of the superior cerebellar peduncle decussate and ascend to the contralateral red nucleus. The infarct also affected the upper pontine tegmentum, immediately ventral to the fourth ventricle, involving the medial longitudinal fasciculus (MLF) bilaterally with greater involvement of the left (Fig. 1).

2. Discussion

WEBINO is a rare disorder characterized by bilateral exotropia on primary gaze, bilateral INO and impaired convergence. It may be associated with other features e.g. vertical gaze palsy, up-beat nystagmus and skew deviation [1,2]. The most common reported etiology is infarction followed by multiple sclerosis and then trauma [2–4]. Other reported etiologies are listed in the Supplementary online table. While the pathobiological underpinnings of the WEBINO syndrome remain a matter of some controversy, the clinical constellation of findings are thought to be derivative of bilateral MLF damage producing bilateral INO, likely in conjunction with abnormalities of the medial rectus subnuclei (MRSN) of the ventral oculomotor nuclear complex culminating in bilateral exotropia and signifying bilateral convergence failure. Since MRSN neurons are scattered within the MLF at the level of the ponto-mesencephalic junction, a lesion at
this level could affect both structures, resulting in the WEBINO syndrome [1,2]. Notwithstanding the WEBINO syndrome has been most commonly reported to be a consequence of mesencephalic lesions, there are reports of isolated pontine lesions causing the syndrome [1–4].

Experimentally, INO and impaired vergence have been induced by injecting lidocaine directly into the MLF despite MRSN preservation [5]. This observation and reports of alternating exotropia indicate that MRSN involvement should not be assumed as the exclusive cause of bilateral exotropia. In particular, this conspicuous feature of the syndrome may also result from paramedian pontine reticular formation overactivity during attempted fixation of the adducted paretic eye [1–3]. Thus, bilateral exotropia in WEBINO may also be a consequence of bilateral paralytic pontine exotropia (PPE).

While neurogenic stuttering (NS) has been associated with PPE [6] and a left INO [7], there has never been any association with the WEBINO syndrome, even within the largest series of WEBINO patients reported to date [1]. Aside from strokes, to date, only progressive supranuclear palsy has been reported to cause either syndrome [3,8] but not both.

The critically-acclaimed movie The King’s Speech portrayed King George VI’s struggle with and triumph over stuttering and drew much attention to this disorder. Stuttering may be developmental or acquired (neurogenic). Developmental stuttering (DS) is a transient dysfluency, occurring in about 5% of children 4 to 5 years of age, marked by initial sound prolongations, word or part-word repetitions, hesitations and silent blocks with or without secondary anxiety-induced behaviors. Ultimately, about 85% of preschoolers develop the neuro-motor skills to overcome it. It is exacerbated by anxiety and is diminished by familiar or automatized formulae. Dysfluency is reduced with repetition, a phenomenon termed the adaptation effect [9].

NS is a rare neurologic disorder reported in the literature for over 100 years and received scarce attention until the 1970s [9,10]. Based on several notable publications [10–12], we propose to define NS as an adult-onset, acquired or re-acquired dysfluency secondary to a brain lesion characterized by involuntary repetitions, prolongations and blocks that is not the result of a disorder of language formulation (i.e. aphasia) or a psychiatric condition.

Unlike DS, the dysfluency is not restricted to initial phonemes, occurs in monosyllabic and polysyllabic words, does not adapt, persists during singing but lacks secondary behaviors and anxiety [3,12,13]. Despite proposed criteria for NS, it remains very challenging to differentiate it from DS based on symptomatology alone [10,12,14]. As such, the most important distinction between the two conditions is phenomologic: NS occurs with a clear precipitating event [13]. In subjects with NS, a history of DS was present in 12% [12] to 14% [14] indicating that adults who had recovered from DS were at greater risk of NS following a brain insult.

Clinically, stuttering should be distinguished from other motor disorders of speech. Logoclonia is characterized by repetition of the last syllable of words; echolalia by automatic repetition of words spoken to the patient [15], and palilalia by compulsive repetition of a word or phrase with ‘palilalia aphone’ (i.e. increasing rate with diminishing loudness) [16].

Lesions causing NS have been reported in all cortical lobes, cerebellum, subcortical white matter, basal ganglia (BG), corpus callosum, thalamus and brainstem. Pontine lesions are uncommon and mesencephalic lesions are even more exceptional causes of NS [6,7,9–14].

The most commonly reported etiology for NS is strokes followed by traumatic brain injury [10,12,13]. Epilepsy, pathologic thalamic discharges, Parkinsonian syndromes, dopaminergic medications and a wide variety of other drugs have also been etiologically-implicated [9,10].

The exact neural circuits involved in NS remain unknown. Human speech production requires an intact and constantly integrating neuronal circuitry of cortico-BG-thalamo-cortico-recticular projections including cerebellothalamic and PAG projections, to control and coordinate the highly precise, dynamic, rapidly fine-tuned, sequential motor movements of the oral articulators (lips, jaw and tongue), respiratory musculature (adjusting inspiration, expiration and subglottic air pressure) and laryngeal activity (modulating vocal fold length and tension) [9,17–19].

A phylogenetically ancient midline neural network centered within the PAG controls visceromotor mechanisms producing involuntary vocalizations. A neocortical system maintains hierarchical control over this visceromotor system to produce volitional speech [17]. Cortical areas important for speech production include the motor cortex, supplementary motor area (SMA), pre-SMA, anterior cingulate cortex (ACC), medial prefrontal cortex (MPFC) and the auditory cortices [9,17,19,20]. While the SMA is important in organizing self-initiated movements [17], the pre-SMA is involved in syllable representation and spatial and temporal serial coordination of the motor apparatus [20].

Cortical efferents converge on the BG; in turn, BG efferents, refined by projections from the brainstem reticular system (BRS) and the

**Fig. 1.** Brain MRI showing an acute midbrain infarction, extending from the periaqueductal gray region to the interpeduncular fossa. Also involved in the midbrain was the area where the fibers of the superior cerebellar peduncle decussate and ascend to the contralateral red nucleus. The infarct also affected the upper pontine tegmentum, immediately ventral to the fourth ventricle, involving the medial longitudinal fasciculus bilaterally with greater involvement of the left.

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cerebellar cortex, project to the thalamocortical network [9]. The BG modulates speech production by inhibiting any extraneous movements and provides species-specific learned motor control and built-in reflex control patterns, indispensible to the production of highly skilled movement sequences required for speech [9].

The thalamic centromedian (CM) nucleus is essential in human speech production and has been described as an interface between the visceromotor and neocortical systems [17]. Ascending BRS projections to the CM nucleus ensure an optimized state of physiologic readiness for the dynamic and synchronized interactions of neural networks involved in speech production [9]. Many metabolic disorders and potentially-sedating medications etiologically-implicated in NS may be secondary to a state of sub-optimal preparedness of this reticulo-thalamo-cortical network.

The PAG, which lies close to the ponto-mesencephalic junction, is critical in vocalization [17,18]. PAG lesions may render both humans and animals mute. Correspondingly, PAG stimulation elicits species-specific vocalizations. The PAG may be an “anatomic Segway” of the descending vocalization-controlling pathway and a relay station for vocal information processing [19] that couples sensory and motivation-processing structures to the vocal motor-coordinating mechanisms [18]. It appears to be responsible for the initiation and intensity of vocalization, not its patterning [19]. As stuttersers often experience blocks with initial phonemes, and more so at the beginning of a sentence, this may implicate dysfunction of the PAG. Indeed, midbrain lesions affecting the PAG have been reported to cause a ‘stuttering-like repetitive speech disorder’ [16], palilalia [15] and NS [6].

In summary, the dynamic interaction between the cortico-BG-thalamo-cortical and midline PAG neural networks modulated by cerebellar and BRS projections, is important in the preparation and rapid motor sequencing of volitional speech. Interruptions at any point in this intricate circuit may compromise the precise synchrony of motor movements essential for speech, and cause stuttering.

3. Conclusion

The WEBINO syndrome in our patient was due a midbrain infarction affecting the MRSN and bilateral MLF. The same infarct resulted in NS by affecting several neural circuits. Involvement of the PAG likely disrupted both its role in the initiation of vocalization and its ability to couple sensory and motivation-processing mechanisms with the vocal motor-coordinating circuit. Interruption of the ascending BRS projections resulted in suboptimal performance of the reticulo-thalamo-cortical circuit, compromising the state of physiologic readiness needed to ensure precise, synchronized motor speech movements. Furthermore, another contributing factor may have been disrupted cerebellar automaticity, evidenced by the presence of left-sided ataxia.


Conflict of interest

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Contributions

Study concept and design (Drs. Beh and Frohman); acquisition of data (Dr. Beh); analysis and interpretation of data (Drs. Beh and Frohman); drafting of the manuscript (Dr. Beh); and critical revision of the manuscript for important intellectual content (Drs. Beh and Frohman).

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