Syndromes Affecting the Central Nervous System

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KEYWORDS

• Lesch-Nyhan syndrome • Marcus Gunn syndrome • Cavernous sinus syndrome • Superior orbital fissure syndrome
• Trotter syndrome • Horner syndrome • Frey syndrome • Ramsay-Hunt syndrome

KEY POINTS

- Many syndromes affecting the central nervous system (CNS) demonstrate both intraoral signs as well as head and neck manifestations.
- Their causes include, but are not limited to, genetics, infection, trauma, neoplasm, postsurgery, and idiopathy.
- Various treatment methods are available and must be considered when working with patients who present with syndromes affecting the CNS.

Lesch-Nyhan syndrome

- Genetics
  - Extremely rare, present in only 1 in 380,000 live births.[1]
  - Lesch-Nyhan syndrome (LNS) is an X-linked recessive disorder of purine metabolism; however, up to 30% of patients carry de novo mutations.[2,3] It is caused by the deficiency of hypoxanthine guanine phosphoribosyl transferase (HPRT), which is a purine salvage enzyme responsible for recycling purine bases into purine nucelotides.[4] Specifically, it converts hypoxanthine and guanine into their respective 5′-mononucleotides.[5]
  - The gene for HPRT (*HPRT1*) is encoded on the long arm of the X chromosome at Xq26-Xq27.[2] This enzyme is present in all tissues with the highest levels in the basal ganglia, which accounts for the extrapyramidal effects seen in this syndrome.[4]
  - Because it is an X-linked disorder, male patients are almost exclusively affected. Female patients may be carriers.[5]
  - A phenotypic spectrum exists, which is thought to be based on variability in HPRT levels and activity.[4,5] Classic LNS is correlated with severe or complete HPRT deficiency. Patients with partial HPRT deficiency may present with hyperuricemia with or without neurologic and/or behavioral symptoms.[4,5]
- Clinical features
  - Often, children have a normal prenatal and perinatal course with development of symptoms within the first 3 to 6 months.[1]
  - LNS has a spectrum of phenotypic presentations. However, classic LNS is characterized by aggressive and self-mutilating behavior (most commonly persistent lip, tongue, and finger biting resulting in severe avulsion injury to perioral tissues and amputation of digits), hyperuricemia, and involuntary movements with severe dystonia (Fig. 1A, B).[2,6,7]
  - Other features that may be present include developmental delay, megaloblastic anemia, nephropathy, and gout or tophi.[2,4]
  - The first sign is the appearance of an orange or reddish sandy material in the diapers of newborns due to uric acid crystalluria and microhematuria.[2,3] Additional early findings, within the first year of life, include episodic opisthotonus and the inability of a child to sit in a chair unless secured with chest or waist restraints (see Fig. 1C).[1,2,7]
- Differential diagnosis
  - Diagnosis is made based on phenotypic presentation, elevated serum uric acid levels (greater than 4–5 mg/dL in children), and HPRT enzyme assays.[2,4]
  - A wide array of disorders of purine metabolism exist that exhibit features of LNS such as gout, Arts syndrome, ribosephosphate diphosphokinase, hyperactivity, and adenylosuccinate lyase deficiency.[1]
  - From a cognitive and neurobehavioral standpoint, LNS may mimic dyskinetic or athetoid type cerebral palsy, autism, Rett syndrome, Cornelia de Lange syndrome, or Down syndrome.[8]
- Treatment considerations for the oral and maxillofacial surgeon
  - Treatment has largely been aimed at controlling the presenting symptoms and prevention of severe injury from self-mutilation.

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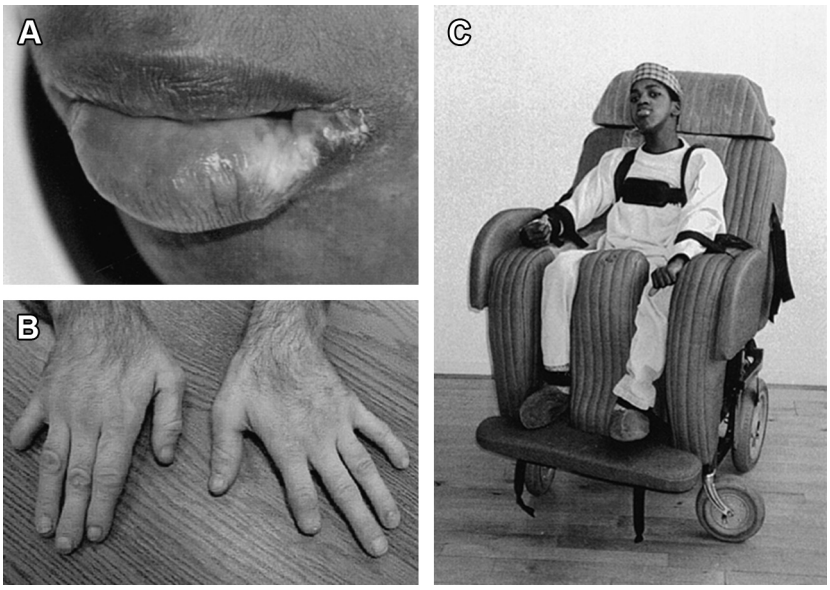

Fig. 1 Self-injury in Lesch-Nyhan syndrome. (*A*) Injury from persistent lip biting. (*B*) Finger amputation from self-mutilating behavior. (*C*) Patient in protective physical restraints and wheelchair device. (*From* Visser JE, Bär PR, Jinnah HA. Lesch-Nyhan disease and the basal ganglia. Brain Res Brain Res Rev 2000;32(2—3):467; with permission.)

- Allopurinol has been used to decrease the overproduction of uric acid.[4] This, in turn, delays the development of renal failure.[6] Allopurinol, however, has no effect on behavioral, neurologic, and cerebral manifestations of the syndrome.[4,6] Dystonia and spasticity have been managed with GABA agonists (eg, benzodiazepines and baclofen), dopamine replacement therapy (eg, L-dopa), and deep brain stimulation to the globus pallidus.[4,6] Control of self-injurious behavior has been sought with benzodiazepines, neuroleptics, antiepileptics, and chloral hydrate.[6] Recent studies have demonstrated that the limitation of self-mutilating behavior includes a combined approach using physical restraints, behavioral treatment, and pharmacologic therapy.[6]
- In the event that self-mutilating behavior is refractory to medical management, alternative therapies have been proposed. Some have advocated extraction of front teeth or all remaining teeth.[6] To avoid this invasive treatment, other investigators have advocated oral protective devices such as lip bumpers or shields, tongue shields, and occlusal bite plates or splints, which have shown some success.[6]
- A recent study by Chen and colleagues[4] demonstrated regression in aggressive and self-injurious behavior and to a lesser extent dystonia with oral supplementation of S-adenosylmethionine based on its therapeutic potential to replenish the nucleotide pool in the brain.

Marcus Gunn syndrome

- Genetics
  - Marcus Gunn syndrome is the most common congenital synkinetic eyelid disorder, with a prevalence of 4% to 6% among patients with congenital ptosis.[9]
  - Several studies have reported that patients have a higher likelihood to have the left eye affected.[10,11] The syndrome was also found to exhibit equal sex predilection.[9]
  - Patients with Marcus Gunn syndrome may also have other eye disturbances such as amblyopia, vertical strabismus, and double elevator palsy. These eye disturbances should be addressed before any corrective ptosis surgery.[9]
- Clinical features
  - Marcus Gunn syndrome, or trigemino-oculomotor synkinesis, occurs due to an aberrant connection between the motor branches of the third division of trigeminal nerve innervating the pterygoid muscle and the fibers of the superior division of the oculomotor nerve that innervate the levator palpebrae superioris.[12]
  - It is clinically characterized as a ptotic eyelid that is rapidly elevated on lateral excursions, opening of the mandible, whistling, sucking, blowing, smiling, speaking, and tongue movements (Fig. 2).[13,14]
- Differential diagnosis
  - A differential diagnosis to consider is Marin-Amat syndrome. This synkinetic eyelid disorder is characterized as involuntary eyelid closure on jaw opening. It occurs due to an aberrant connection between the facial nerve and the trigeminal nerve.[15]
- Treatment considerations for the oral and maxillofacial surgeon
  - Eye shields or eye protection should be used during dental or oral and maxillofacial surgery procedures because the eye will open when the mouth opens.[13]
  - In a mild case that is not bothersome to the patient, no intervention can be elected.
  - In a case in which there is moderate-to-severe ptosis, or if the patient has esthetic concerns, a surgical intervention can be considered.
  - Several corrective procedures exist, including the Fasanella-Servat procedure, bilateral levator muscle excision followed by bilateral fascia lata brow suspension, or bilateral frontalis suspension with levator