Serotonin Mediated Cluster Headache, Trigeminal Neuralgia, Glossopharyngeal Neuralgia, and Superior Laryngeal Neuralgia with SAD Chronicity

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ABSTRACT: Cluster headache is a rare and severe pain syndrome with elusive pathophysiology. Serotonin pathways within the brainstem may be implicated in cluster headache with seasonal affective disorder and a subset of cranial nerve neuralgias. We describe and chronicle a syndrome consisting of cluster headache, seasonal affective disorder, with associated trigeminal, glossopharyngeal, superior laryngeal neuralgias in an 11-year-old female. Pharmacologic interventions for this patient were examined in conjunction with current classification, location and function of serotonin receptors. Etiology is postulated as mixed cranial nerve excitation via endogenous 5-HT (agonist) activity of 5-HT_3 receptors within the nucleus tractus solitarius and trigeminal tract nucleus.

KEY WORDS: Cluster Headache; Trigeminal Neuralgia; Glossopharyngeal Neuralgia; SAD; Fluvoxamine; 5-HT_3.

Introduction

Serotonin is a major neurotransmitter known to mediate mood, satiety, and pain perception. A seasonal or other shift in sunlight can trigger a decline in melatonin resulting in diminished serotonin production.[1] Low serotonin levels have been strongly implicated in cluster headache (CH) and seasonal affective disorder (SAD).[2] SAD and CH have been associated with a shared seasonal onset.[3] A seasonal trigger

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may be suggested in a subset of facial cranial neuralgias.[4] The latter neuralgias often respond to anti-depressant therapy and involve cranial nerves V, IX, X or XI.[5] Notably, both the trigeminal tract nucleus, subserving cranial nerve V, and the adjacent nucleus tractus solitarius (NTS), subserving cranial nerves IX, X and XI are densely packed with serotonin receptors.[6]

Triggers occur with many of cranial nerve neuralgias, especially trigeminal neuralgia, and remain specific for the individual patient. Cranial nerve neuralgias sometimes occur in pairs.[5,7] The chronicity of CH and SAD has been associated with a shared seasonal onset.[3] The combination of CH, SAD, and cranial nerve neuralgias has not been previously reported. We describe such a case occurring in a pre-adolescent girl.

Cluster headache (CH) is considered the most painful of headaches currently classified.[8] CH occurs more frequently in males (5:1–9:1). The peak age of onset is 20–29. The childhood presentation of CH may be misinterpreted, resulting in under reporting of the illness within the pediatric population.[9] Ten to twenty percent of CH patients exhibit the chronic form defined as recurrent pain greater than one year in duration with remissions of less than 14 consecutive days.[4] The intense pain is habitually unilateral at or around the orbit in a V_1 distribution. Nasal stuffiness and hyperactivity with head banging or rubbing accompanies the onset of pain. Typically ocular Horner's syndrome with supraorbital swelling, ipsilateral ptosis, miosis, tearing, and conjunctiva injection follows the pain episode. Tearing may precede the pain episode.[4] Speech remains intact. In a minority of cases structural abnormalities may be identified by neuroimaging. CH attacks frequently occur within the same hours of the day over the course of several weeks.[8] CH pain first occurs in the daily cycle at the onset of REM sleep, 1–1 1/2 hours after retiring. Sleep deprivation has been effective in delaying CH attacks into the early morning hours but not eliminating the nocturnal attack. Decreased levels of serotonin and nocturnal melatonin are reported in cluster headache patients. Seasonality of this pain syndrome has been described and correlates with the active phase in SAD patients.[1]

SAD is typically characterized by recurrent depression with a fall/winter onset, hypersomnia and overeating.[10] Five to ten percent of the U.S. population has symptomatology suggestive of the disorder, and up to 3%–4% of U.S. school age children may suffer from SAD.[11] Serotonin levels are decreased in SAD patients.[2] 5-HT_7 serotonin receptors are thought to play a role in circadian rhythms.[6]

Trigeminal neuralgia involves the excitation of one or more of the three branches of the trigeminal nerve. Less than 5% of trigeminal neuralgias involve V_1.[4] The pain episodes are commonly unilateral and are of sudden onset with short duration. Repetitive episodes occur daily. The pain does not cross to the contralateral side. Carbamazepine, Phenytoin and Clonazepam have shown clinical efficacy, and are withdrawn after a short course. Remissions occur spontaneously and may last for months to years. Trigeminal neuralgia occurs more frequently in women (3:2) and is 100 times more common than glossopharyngeal neuralgia.[5] Trigeminal neuralgia may accompany glossopharyngeal neuralgia in one out of every eight cases.[7]

Glossopharyngeal neuralgia involves unilateral irritation of the ninth cranial nerve (IX). Sensory vagal nerve afferents are also suspected in this pain syndrome. Symptomatology includes painful, cutting, stabbing, shooting or sharp sensations to the throat. Throat pain can last minutes to hours. Ipsilateral ear sensations include "fullness" or "dragging" and usually occur prior to the pain episode in the throat. A foreign body feeling on the ipsilateral tonsil during or prior to pain onset has been reported.[7] Triggers include swallowing, talking, yawning, and coughing.[5] Activation of the dorsal motor nucleus of the vagus nerve (X) during a glossopharyngeal neuralgia episode has resulted in bradycardia and syncope.[7,4]

Superior laryngeal neuralgia is a rare pain syndrome associated with lowered pitch and pain on vocalization, lateral throat pain occurring within the submandibular region. Pain may also present under the ear. Pain episodes can last minutes to days. Activation of the superior laryngeal nerve occurs via the general visceral afferent component of the vagus nerve. Sufferers have identified triggers.[5]

Case Report

D. is an 11-year-old female presenting with a three-year history of chronic cluster headache and SAD. Accompanying neuralgias included trigeminal neuralgia, glossopharyngeal neuralgia, and superior laryngeal neuralgia. Her symptomatology increased with seasonal decrease in day length. CH first presented upon relocation from Georgia (33.47 N latitude) to Michigan (42.32 N latitude) in late summer, during the child's ninth year. The chronic form of CH was established after unsuccessful withdrawal of maintenance medication in the second year. Triggers have included Dihydroergotamine mesylate (Migranal), repetitive but undeniable yawning, and inhalation of CO_2. Pharmaco-

logic outcomes for this patient were examined in conjunction with current classification, location and function of serotonin receptors.

Patient History

Patient D. was born via induction at 43 weeks gestation. As a toddler she experienced gross motor and language delays speaking 3–word sentences at age 5 and toe walking until age 8. After speech development, complaints of urinary urgency, fear of poisoning, and fear of death occurred on a fall/winter cycle. At age 5 she developed repetitive spitting behavior and complained of occasional head pain. Anxiety and physical symptoms progressively increased each fall/winter season. All school photos taken in the fall/winter seasons show supraorbital swelling and facial asymmetry on the left. At 7 years 8 months the Wechsler's Intelligence Scale III for children was administered. The assessment revealed a full scale IQ of 126; with verbal and performance scores of 131 and 116 respectively. At age 8 patient D. reported a transient loss of color vision. The loss of color vision correlated with "seeing harmful snakes and spiders" and right sided chest pain with increased pulse. Fluvoxamine (Luvox) 25mg was instituted. A good response from Fluvoxamine occurred without dose elevation for two years. Family history includes bipolar disorder, unipolar depression, obsessive compulsive disorder, anorexia nervosa, and tic douloureux.

The first "active phase" for CH occurred in the fall/winter of 1997. At age 9 the patient relocated from Georgia (33.47 N latitude) to Michigan (42.32 N latitude). She was slowly tapered off Fluvoxamine over the course of one month, ending on October 31. "Terrible head pain" occurred seven days after her last dose of Fluvoxamine. Twenty-one days post Fluvoxamine therapy, patient developed left-sided cluster headaches, Horner's syndrome and polydipsia during the pain episode. Brain MRI and MRA were negative for related pathology. After a trial course of Indomethacin failed to alter the headache course, standard induction therapy with Prednisone 40mg/day for 4days was instituted. Fluvoxamine 25mg/day was restarted as maintenance therapy. Oxygen at 4liters/min via nasal cannula constituted abortive therapy. Once stabilized, the patient further recovered in Florida at 26.52(N) latitude. Her last reported CH of the first active phase was on December 31, 1997.

In late June 1998 Fluvoxamine was tapered over 5 weeks. Concurrent, progressive dose replacement equivalent of Fluoxetine (Prozac) therapy at 20mg/day was completed by August. The first CH occurred on day 15 of the Fluvoxamine taper. The CH pattern accelerated, bilateral facial flushing with pain or numbness was noted during or shortly after a pain episode. The antihistamine Periactin (at 4mg/day) provided no relief. Migranal nasal spray was added to the patient's CH protocol, for abortive therapy. Ergotamine (Migranal) has serotonin antagonist properties.[12] A single dose of Migranal during a CH episode produced acute symptoms. These included: sudden nausea with vomiting, bilateral facial flushing, increased heart rate (140/min), sore throat with foreign body sensation, pain upon vocalizing, "narrowing of throat" and "dragging string" through ear canal sensation (right side), and the inability of the patient to turn her head to the left. Her CHs occurred at the same times

of day as in the previous season. CH and cranial neuralgia episodes continued to increase. The patient was removed from Fluoxetine, completing 12 weeks of therapy. Fluvoxamine 25mg was re-instituted and 4 weeks later CH, with accompanying cranial nerve neuralgias V, IX, X, and XI resolved. A repeat brain MRI/MRA was performed with incidental finding of a left cerebellar hemisphere development venous anomaly (venous angioma). MRI/MRA of the neck was unremarkable.

The patient remained asymptomatic on Fluvoxamine 25mg/day until mid-November 1998. Repeated episodes over a six week period included: hypertension, chest pain, back pain, bilateral facial flushing, increased facial temperature/facial pain, extreme sudden nausea with/without vomiting, dizziness, throat pain, "voice pain," half of tongue base "disconnected," and "string dragging" in ear, escalated in number and acuity. Yawning was identified as a trigger for trigeminal neuralgia at V_2 (facial flushing) cascading into glossopharyngeal neuralgia and superior laryngeal neuralgia. Cranial neuralgias would often occur shortly before or after a cluster headache episode. A visual decrease in color intensity but not hue was reported during pain episodes. Triggers included Migranal, repetitive but undeniable yawning and inhalation of CO_2. In the course of fall/winter the patient was seen in the ER three times for pain episodes related to cluster headache with cranial neuralgias. Sumatriptan nasal spray and oral preparation were initially used with good relief, but over time chest pain and rebound neuralgias occurred with shortness of breath. Three courses of IV steroid treatment were given without benefit. Neurontin 300mg/tid was prescribed but discontinued on day 4, due to ataxia, muscle weakness and persistent neuralgias. Fluvoxamine was increased to 50mg/day. Carbamazepine (Tegretol) was given at a starting dose of 100/bid then substituted for Tegretol XR 200mg/bid. Anti-seizure therapeutic levels were reached and maintained at this dose. CH symptomatology increased with progressive decrease in day length, following the SAD predictive model.[3] Patient D. was relocated to Florida (26.52 N. latitude) for two weeks. Treatment upon return to Michigan included 10,000 lux light box therapy bid. Symptomatology continued to increase with CH and cyclic cranial nerve neuralgia episodes. In February the patient was relocated to the British West Indies (19.30 N. latitude) for one week with significant improvement. Symptomatology accelerated upon return to Michigan but gradually decreased with increasing day length. Removal from Tegretol ensued by slow taper ending May 1. The patient remained asymptomatic on Fluvoxamine 50mg/d, during the spring/summer season, with the exception of a single episode of trigeminal and glossopharyngeal neuralgia, occurring after three dark and raining days in April.

In mid-September 1999, sudden nausea preceded the almost daily CH and cranial nerve neuralgia episodes. In early November, Fluvoxamine 50mg/day was gradually increased to 100mg/day. Symptomatology continued to increase in frequency. Amitriptyline (Elavil) with escalating dosage to achieve 50mg/day was instituted in mid-November. Ten days following augmentation of selective serotonin reuptake inhibitor (SSRI) therapy with tricyclic antidepressant therapy (TCA) the patient was asymptomatic. At one-month post-TCA therapy the patient reported one episode of glossopharyngeal neuralgia. EKG

and Amitriptyline levels were monitored. The patient retreated to Florida for 3 weeks beginning on December 16, 1999 and remained asymptomatic upon return to Michigan.

Discussion

Postulated Mechanism of Syndrome

High densities of 5-HT_3 receptors are found in the NTS, trigeminal tract nucleus, dorsal vagal complex, and the hippocampus in man.[6] Rapid depolarization and subsequent excitation of central nervous system serotonin neurons within the NTS, trigeminal nucleus and dorsal vagal complex is hypothesized as the mechanism for the CH variant described.

Depolarization of 5-HT_3 receptors can occur through the introduction of Na+, K+, and Ca++ ions or via endogenous 5-HT agonist activity.[6] Endogenous 5-HT that exceeds physiologic neuronal limits (a 5-HT spike) acts as a 5-HT_3 receptor agonist. Extracellular serotonin agonist activity is commonly seen in chemotherapy patients. Upon Cisplatinum administration endogenous 5-HT is introduced to 5-HT_3 receptors within the NTS, from enterochromaffin cells in the small intestine. The sudden availability of 5-HT in excess of extracellular concentrations seen in neuronal uptake and synthesis regulation acts as an agonist exciting the NTS and eliciting sudden emesis commonly associated with most antineoplastic agents.[13]

Blockade of serotonin uptake by a serotonin antagonist will produce a significant and sudden increase in endogenous 5-HT. Migranal (dihydroergotamine) is a serotonin antagonist. Migranal's serotonergic activity is postulated to precipitate the activation of 5-HT_3 receptors within the NTS and trigeminal tract nucleus, via an endogenous 5-HT spike.

Cranial nerves V, IX, X, XI can be activated by 5-HT_3 receptors within the NTS and trigeminal tract nucleus.[14] Rapid depolarization of the lower NTS subserving the general visceral afferent component of the glossopharyngeal, accessory and/or dorsal vagus nerves may result in cranial nerve neuralgias of IX, X, and/or XI. Rapid depolarization of the lower and middle tracts of the trigeminal tract nucleus may respectively result in the excitation of the first and second branches of the trigeminal nerve leading to CH and trigeminal neuralgia. 5-HT_6 and 5-HT_7 receptors in the hippocampus and hypothalamus may play

a role in the patient's yawning trigger and altered circadian rhythm respectively.[6] Taste, subserved by the upper portion of the NTS, was not altered in this patient. (See Figure 1)

Conclusion

Activation of 5-HT_3 serotonin receptors within the NTS and trigeminal tract nucleus via endogenous 5-HT agonist activity is postulated as the mechanism and neuroanatomic basis of the described serotonin mediated CH variant.

Decreased extracellular serotonin noted in SAD patients may create a seasonal decrease in baseline serotonin. Endogenous 5-HT agonist activity is more readily achieved in the fall/winter months when diminished levels of baseline serotonin occur.

Management of this syndrome includes down-regulation of serotonin receptors with SSRI therapy augmented by TCA therapy. A decreased firing rate of 5-HT_3 serotonin neurons within the NTS and trigeminal tract nucleus with concurrent/compensatory increases in baseline extracellular 5-HT was achieved with Fluvoxamine and Amitriptyline.

Fluvoxamine proved superior to Fluoxetine at corresponding doses. Both Fluvoxamine and Fluoxetine inhibit serotonin reuptake at 5-HT_3 receptors. This increases extracellular serotonin, down-regulating the 5-HT_3 receptor. Fluvoxamine additionally inhibits serotonin reuptake at 5-HT_{1A} receptors (β adrenergic receptors).[15] This further increases extracellular serotonin levels augmenting the down-regulation of 5-HT_3 receptors. By raising the activation threshold of 5-HT_3 receptors in the NTS and the trigeminal tract nucleus we postulate SSRI's alone or augmented with TCA's may reduce the aberrant 5-HT agonist activation.

Summary

CH is rarely diagnosed in children.[9] We examine a pediatric case of CH, SAD, and accompanying cranial nerve neuralgias. Location and function of 5-HT_3 receptors in addition to neuroanatomy of cranial nerves V, IX, X, XI at their termination point within the trigeminal tractus nucleus and NTS is reviewed. Etiology for this CH variant is hypothesized as 5-HT_3 serotonin receptor activation of NTS and tri-

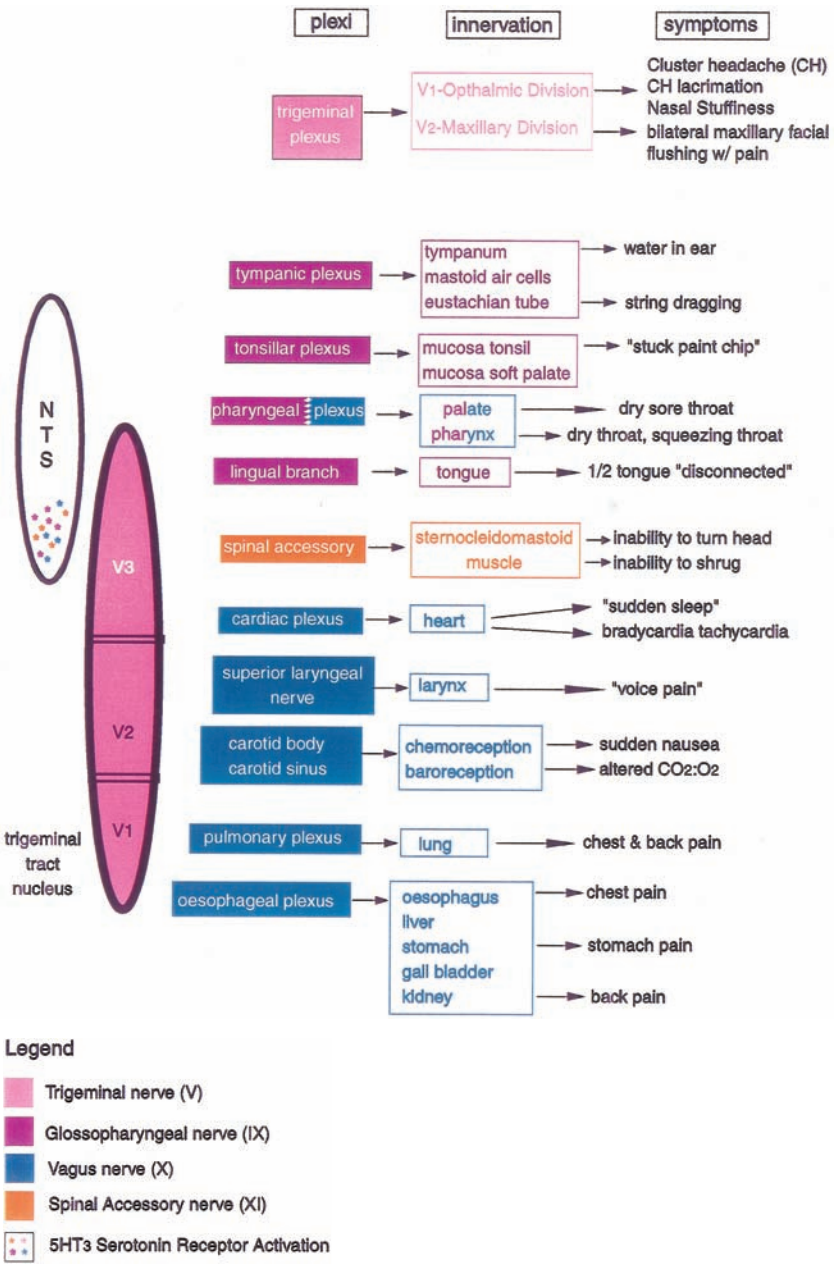

Figure 1. NTS and Trigeminal Tract Nucleus 5 HT_3 Receptor Distribution, Pathways and Related Symptomatology

geminal tractus nucleus within the brainstem. Pharmaceutical management of this serotonin mediated syndrome with SSRI (Fluvoxamine) maintenance therapy in addition to TCA therapy (Amitriptyline) during the active phase is outlined. The treatment course is proactive, year round, and adjusted for the length of day. Pain management with oxygen and travel to decreasing northern latitudes appears beneficial. Should the need arise, 5-HT_3 antagonist therapy, with Ondansetron (Zofran) to counter acute activation episodes of the NTS and trigeminal tract nucleus, might be considered. The future challenge for clinicians and researchers alike will be in fully understanding the biochemical pathways, circadian rhythms, and seasonal shifts, leading to such extraordinary pain syndromes, depression and anxiety disorders. Such knowledge could eliminate or minimize symptomatology by preempting serotonin-mediated disorders with proactive treatment plans, in susceptible populations.

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