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**Medicine in the future - with subspecialists in medullary neurology and brain dentistry**

Jaster JH. Medullary neurology and brain dentistry

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**Abstract**

The solitary tract nucleus of the medulla with its limited watershed vascular capacity may occasionally be the focus of transient ischemia caused by the increased metabolic demands associated with frequent and intense neuronal stimulation from other organs and other parts of the brain. Case reports have suggested that these ischemic changes may sometimes result in the initiation of intense autonomic discharges, which can occasionally be fatal. Therapeutic interventions for the medulla oblongata are hampered by its limited accessibility. Systemically administered pharmaceuticals may have some usefulness in future years. Previous experience with vagus nerve stimulation in the treatment of epilepsy suggests that it may have some usefulness in stabilizing medullary autonomic discharges. Computerized electronic stimulation of other cranial nerves may be helpful as well, especially the chorda tympani nerve, and may be most easily accomplished from implanted dental appliances, especially molar modules, transmitting signals *via* secondary transmitters procedurally placed on cranial nerves. Future technology may enable wireless signaling from the implanted dental appliance to the secondary transmitter placed at the nerve site. By the year 2050 subspecialists in Medullary neurology and brain dentistry may use computerized electronic stimulation of cranial nerves to prevent sudden unexpected death and treat “chest pain from the brain”.

**Key words:** Solitary tract nucleus; Ischemic autonomic umbra; Medulla oblongata; Molar module; Chorda tympani nerve; Medullary brain lesion; Medullary neurology; Chest pain from the brain; Sudden unexpected death; Brain dentistry; Vagus nerve stimulation

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**Core tip:** Medical investigators in the 21st century have reported numerous cases in which the presence of a small medullary brain lesion was associated with sudden unexpected death. Many such medullary lesions have otherwise produced only minor clinical symptoms and have in themselves been previously considered relatively harmless. Many victims have been considered healthy prior to sudden death, and the medullary brain lesions were incidental discoveries at autopsy, with no other causes of death identified.

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**MEDULLARY NEUROLOGY**

Medullary neurology, as described here, is a branch of medical science concerned with the medulla oblongata and its disorders. The term may bring to mind the work of several 19th century neurologists, such as Wallenberg, who described stroke syndromes resulting from occlusive vascular disease affecting different parts of the vertebro-basilar artery system and sometimes related to syphilis. Some of those infarctions involved autonomic fibers located in the medulla oblongata, and resulted in focal autonomic deficits involving the face. Also described in that era was medullary brain irritation resulting in fulminant systemic autonomic phenomena affecting thoracic organs. In 1861 Brown-Séquard discussed his own clinical observations in the context of then recent laboratory reports by physiologists that “sudden irritation of the medulla oblongata often produces arrest of the heart’s action”, but that this can be blocked by sectioning of the vagus nerve[1].

The concept of “occlusive cerebrovascular disease as a cause of strokes” subsequently flourished in clinical practice, and the names of those 19th century investigators remain in today’s medical lexicon as eponyms for specific neurological deficits. But the concept of “medullary irritation as a cause of fulminant systemic autonomic phenomena” smoldered and never caught fire. Certainly when someone drops dead unexpectedly in the year 2015, the last thing that anyone considers as a possible cause of death is a cardiac arrest resulting from medullary irritation from a small medullary brain lesion in the absence of hemorrhage or mass effect.

That may be about to change - not because medullary brain lesions, as traditionally defined, are so common, but because our traditional clinical concepts regarding ischemic lesion formation in the brain medulla fail to acknowledge its dynamic interactions with the heart, other organs, and other parts of the brain and particularly that those interactions in themselves may occasionally initiate the formation of focal ischemic medullary brain lesions by exciting some areas of the medulla beyond the fixed capacity of their watershed vasculature to supply metabolic nutrients.

**SUDDEN DEATH**

Medical investigators in the 21st century have reported numerous cases in which the presence of a small medullary brain lesion was associated with sudden unexpected death. Many such medullary lesions have otherwise produced only minor symptoms and have in themselves been previously considered relatively harmless. Among the most common, and pathologically benign, were those caused by small infarctions, sometimes associated with diabetes, hypertension, and sleep apnea. But a wide variety of infectious and inflammatory illnesses, as well as multiple sclerosis, have been discovered involving the brain medulla in the setting of sudden unexpected death[2]. Excluded, however, from this phenomenon were large brainstem hemorrhages, infarctions, and compressive lesions, all otherwise long known to cause sudden death.

Clinical cases of sudden unexpected death related to medullary brain lesions, specifically following cardiac arrest[3-7] or following respiratory arrest[8-17] have been reported in approximately equal numbers[2], and all age groups have been involved[2]. In many descriptions of sudden unexpected death related to medullary brain lesions the victims had been considered healthy prior to death, and the medullary brain lesions were incidental discoveries at autopsy, with no other causes of death identified. Pathological findings suggest that sudden unexpected death related to medullary brain lesions is most commonly related to lesions which include specific anatomical regions within the medulla: the solitary tract nucleus in all age groups[10,18,19], and several additional medullary areas specifically in infants[20-22]. The solitary tract nucleus is a medullary autonomic recipient of sensory afferent impulses from organs in the chest and abdomen through the vagus nerve, and it is also involved in the sensation of taste in the anterior tongue through the chorda tympani nerve. Anatomical medullary brain lesions have been thought to induce physiological autonomic abnormalities resulting in sudden death. The mechanism is unknown[8].

Pathological findings from a large number of cases taken together have led some investigators to suggest that sudden infant death syndrome may be a subset of sudden unexpected death related to medullary brain lesions[3,23-25]. This implies that biochemical medullary brain lesions may also induce physiological autonomic abnormalities resulting in sudden death, in as much as an abundance of sudden infant death syndrome research in recent years has focused on medullary neurotransmitter abnormalities, especially involving serotonin[26]. Similarly in adults, a recent neuropathology study[27] of sudden death in various subpopulations of multiple system atrophy found that depletion of medullary serotonergic neurons was associated with sudden death, the leading cause of death in multiple system atrophy. And while studying seizure disorders, a few investigators have speculated that sudden unexpected death in epilepsy may also be a subset of sudden unexpected death related to medullary brain lesions[2] based in part on the autonomic stigmata of associated seizure activity, including central apnea and laryngospasm[8,17,28].

**CHEST PAIN FROM THE BRAIN**

Sudden death probably occurs infrequently compared to the many non-fatal manifestations of abnormally functioning autonomic nuclei related to small medullary brain lesions. Non-fatal events may be experienced by patients as symptoms in the chest, abdomen[7], and elsewhere; yet in these instances the primary illness is located in the medulla and not in the organ where symptoms are experienced. Symptoms may include nausea and vomiting[29], pain in the chest or epigastrium[7], and shortness of breath[13,15]. An occasional manifestation is Ondine’s curse, a syndrome of sleep apnea with preserved wakeful voluntary control of respiration occurring after some medullary infarctions[16]and in association with other types of medullary lesions[12], including medullary plaques in multiple sclerosis patients who subsequently died during their sleep[9]. Most patients with medullary brain lesions will likely not experience sudden death, but the risk of sudden unexpected death in patients with medullary brain lesions is unknown.

**ISCHEMIC AUTONOMIC UMBRA**

The findings of case reports suggest that in some medullary autonomic nuclei, focal areas of parenchymal tissue, often dendritic, may become ischemic when excessive neuronal stimulation results in transiently elevated metabolic requirements exceeding levels that can be supported by the perfusion generated from maximum vascular flow in a fixed watershed area. Such focal medullary ischemia and infarction are often not related to vascular occlusion, or to vascular disease in general, as much as to a mis-match of accentuated metabolic activity and vascular flow which is insufficient in this somewhat unusual physiological setting. Small vessel disease, however, related to diabetes or hypertension may be a contributor. As evidence of watershed vascular insufficiency, investigators have reported small infarctions in watershed areas of the solitary tract nucleus[10,19].

Such pathological findings suggest that increased metabolic requirements and the formation of medullary ischemic lesions may be induced by repetitive neuronal stimuli originating in autonomic sites outside of the medulla, such as during intermittent episodes of heart failure[10,19]. Some focal dendritic sites on medullary autonomic nuclei capable of receiving visceral sensory stimulation *via* afferent neural pathways may experience the formation of ischemic lesions when this stimulation becomes persistent and repetitive. At the convergence of a limited vascular capacity and accentuated metabolic requirements is the spatial distribution that might be called an “ischemic autonomic umbra”, the converse of an ischemic penumbra. Chronic and severe neuronal bombardment from outside the medulla may in some instances result in the formation of a small anatomical ischemic lesion or infarction, which may then itself trigger a significant systemic physiological event involving thoracic organs, possibly fatal, or possibly not[10,19].

**PATIENT CARE**

In today’s world many patients with medullary autonomic lesions would never receive a neurological evaluation because their symptoms would not seem appropriate for referral to a neurologist. Additionally, the clinical recognition of medullary autonomic lesions often does not fit the traditional clinical neurology construct of identifying deficits in motor function, sensory function, or cognition, all of which may remain essentially normal in these patients. And medullary brain imaging is often not helpful due to bony artifacts and inadequate resolution capability.

In the year 2050 patients with chest and abdominal complaints will probably undergo evaluation specific to those areas, just as they would today. But if testing is negative, some will likely be considered candidates for medullary brain evaluation. Initial diagnostic testing of the patient possibly by magnetic resonance imaging, [positron emission tomography,](http://en.wikipedia.org/wiki/Positron_emission_tomography) ultrasound, nuclear medicine, and/or other modalities available at that time will establish a profile of initial conditions within the brain medulla regarding lesions, general tissue architecture, and regional blood flow patterns. A computerized 3-dimensional reconstruction of this information will prepare the patient for treatment, which may include brain dentistry, following any acute management that might be necessary. Essential to the development of medullary neurology will be advances in non-invasive radiology that will yield 3-dimensional dynamic imaging of both medullary parenchymal tissue and medullary vasculature in significant detail, exceeding the resolution capability that is available today.

**BRAIN DENTISTRY**

In the context of medullary neurology, computer-assisted dental applications may become important for two reasons. First, some of the sensory input that terminates in medullary nuclei begins in the peri-dental and peri-oral anatomy, just as some peri-oral motor activity emanates from medullary motor nuclei. And second, the relative proximity of the mouth to the brain together with its accessibility makes the mouth a location in which to install implantable appliances that might potentially be used to enhance medullary blood flow, stabilize electrical activity in the medulla, and perform other functions as well. Brain dentistry, as described here, is a branch of medical science concerned with using dental applications in the treatment and monitoring of brain disorders.

**ELECTRICAL STIMULATION**

As a precursor of brain dentistry, the use of electrical stimulation in the management of neurological illness is still in its infancy but has attained several important milestones. Brain dentistry will likely begin by utilizing electrical stimulation of cranial nerves and building on the experience gained from the use of vagus nerve stimulation. Vagus nerve stimulation has been successfully used in the treatment of epilepsy; and in epilepsy patients it has also been shown to increase blood flow in the medulla as well as in other areas of the brain[30]. Many sensory autonomic afferent fibers of the vagus nerve begin in the chest and abdomen and terminate in the solitary tract nucleus in the medulla. Vagus nerve stimulation follows those fibers to this critical area, and then apparently goes on to stabilize electrical activity throughout the cerebral cortex to prevent seizure activity by a mechanism yet unknown.

Corroborating this is an animal study in which the solitary tract nucleus was electrically stimulated directly, resulting in increased cerebral blood flow as well as enhanced synchronization of the electroencephalogram[31]. And another animal study showed that vagus nerve stimulation significantly reduces the size of induced brain infarction by an unknown mechanism which is nonetheless independent of increased cerebral blood flow[32], thereby implying an additional mechanism of neural protection. In light of these findings it may not be surprising that direct electrical stimulation of the cerebral cortex[33] in animals protects that cortex from induced ischemia by mechanisms that are antiapoptotic, angiogenic, and anti-inflammatory. But more important to brain dentistry may be the indirect stimulation of a specific area of brain tissue by functionally stimulating peripheral nerves that lead to that specific area; and animal studies have shown this to significantly reduce the size of induced infarctions[34].

**MOLAR MODULE**

By the year 2050 “molar modules” may be among the most widely used dental appliances for brain dentistry in adults, due in part to the relatively large size of molars, as well as their posterior position in the mouth. An implanted molar module might consist of a permanent intraosseous metallic hardware casing which could hold computer chips and/or software that could be removed, updated, and replaced *via* a removable extraosseous dental crown. The site of implantation on the alveolar ridge would maintain the integrity of the dental arch and be consistent with overall dental health and dental occlusion. The molar module might fill a space previously made available by the extraction of teeth. Although there has been no previous experience using molar modules or brain dentistry in either animal models or humans, their usefulness is very plausible.

**CHORDA TYMPANI NERVE**

Brain dentistry may utilize computerized electronic stimulation of the chorda tympani nerve *via* a submucosal wire from the molar module to a site where the chorda tympani nerve runs together with the lingual nerve. This is a site frequently used by dentists for the blind injection of local anesthetic agents to anesthetize one side of the tongue together with the adjacent gingiva when performing procedures on the mandibular teeth. The chorda tympani nerve mediates taste sensation from the anterior 2/3 of the tongue, and is largely an innocent bystander for purposes of the dental injection.

Stimulation of the chorda tympani nerve indirectly stimulates the rostral third of the solitary tract nucleus in the medulla *via* functional connections, just as vagus nerve stimulation indirectly stimulates the caudal 2/3 of the solitary tract nucleus. Stimulation of the chorda tympani nerve would also indirectly stimulate the superior salivatory nucleus of the medulla *via* fibers which innervate the submandibular and sublingual glands in the floor of the mouth. Both vagus nerve stimulation and chorda tympani nerve stimulation may ultimately be utilized as treatment modalities in medullary neurology.

The development of wireless communication between the molar module and a secondary transmitter placed at the nerve site would minimize the invasiveness of the procedure to place a secondary transmitter and might open the possibility of blind transmucosal or percutaneous injection of a very small secondary transmitter, inasmuch as a wire connecting it to the molar module would be unnecessary.

Molar modules might eventually be multifunctional with roles in both monitoring and therapy. Cardiac rhythm and local tissue chemistries might be recorded and transmitted to a remote data base or mobile device. Synchronized stimulation of the auditory nerve by sub-audible sound pulses would indirectly stimulate the cochlear nucleus in the medulla. Future research will determine the value of these potential therapeutic modalities and others[35-37]. Some of the potential general goals of brain dentistry are to provide neural protection to vital centers of cardiac and respiratory function and to enhance their performance by optimizing blood flow, preventing ischemic injury, and enhancing electrical stability.

**RECENT RELEVANT RESEARCH**

Firstly, there have been no research publications regarding brain dentistry specifically - but medical investigators have recently been studying ways to prevent sudden deaths in vulnerable patient groups that have relevance to events in the medullary autonomic nuclei. The results of an international trial studying prevention of sudden death and near-death cardiac events in 1325 patients who had heart failure with central sleep apnea[38] have recently been reported. In this trial the patients were given a treatment which augmented pulmonary ventilation nocturnally and presumably improved systemic blood gasses nocturnally. The study, however, ignored the issues of neuro-electrical instability in the medullary autonomic nuclei, and it ultimately concluded that the ventilatory assistance given to the patients did not improve their outcomes, but in fact worsened them[38].

An alternative therapy under investigation is phrenic nerve stimulation. A recent international trial of only 57 patients with central sleep apnea who received unilateral phrenic nerve stimulation[39] showed that it was both safe and effective, even for those who also had heart failure. Although primarily a motor nerve (to the diaphragm), the phrenic nerve carries both sensory and autonomic fibers as well. Phrenic nerve stimulation may possibly have a modulating effect on medullary autonomic nuclei, which might help to prevent adverse cardiac events and improve patient outcomes.

Lastly, to the extent that vagus nerve stimulation is a proposed preventive therapy for sudden unexpected death related to medullary brain lesions, it might be expected to reduce or eliminate the incidence of sudden unexpected death in epilepsy in the intractable epilepsy patients who receive it as treatment. But a recently published study[40] of 466 patients showed that vagus nerve stimulation did not influence the incidence of sudden unexpected death, although its data were collected between 1995 and 2010 and reflected the technology and methods of that time-frame[40].Other investigators[41] of vagus nerve stimulation in epilepsy patients, however, have reported a favorable cardiac electrical stabilization, which encourages further research and only very limited research has been done regarding the specific electronic parameters for stimulation of either the vagus or phrenic nerves, and this could greatly influence outcomes. Much more research is needed.

**CONCLUSION**

Vagus nerve stimulation has been used with relative safety and effectiveness to treat epilepsy, whereby it is thought to stabilize electrical activity in the brain and has been shown to increase blood flow in the medulla. Vagus nerve stimulation indirectly stimulates the solitary tract nucleus, an autonomic site most often involved in cases of sudden unexpected death related to medullary brain lesions, and where blood flow and electrical stability have been called into question.

It is plausible that vagus nerve stimulation might be used in the prevention of sudden unexpected death related to medullary brain lesions as well as non-fatal symptoms, such as “chest pain from the brain”, possibly caused by ischemia and electrical instability in medullary autonomic nuclei. In future years, electrical stimulation of the chorda tympani nerve may be used to indirectly stimulate the solitary tract nucleus with the same goals.

A vast frontier within a small space, the medulla oblongata will likely be the focus of some of the most significant medical advances of the 21st century. Brain dentistry will probably play an important role in both monitoring and therapy related to the brain in general as it accompanies the development of medullary neurology.

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