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The Slow-Brainstem Syndrome: Tinnitus and Dyssynchrony in the Central Nervous System

Claus-F. Claussen

Neurootological 4-G-Forschung Research Institute, Bad Kissingen, Germany

Abstract: Among older patients we regularly find those who complain of a hazy tinnitus in combination with vertigo, giddiness, and dizziness. They also report a reduced state of alertness. Objectively, these patients exhibit an increase in latencies of experimentally evoked vestibular nystagmus and of auditory brainstem-evoked potentials. This group of patients is affected by the disorder known as *slow-brainstem syndrome*. By evaluating therapeutic responses, we noted especially in this group that a combination of cocculus (picrotoxin), conium (Coniine), amber, and petroleum (Vertigoheel) has a "tune-up" effect on the brainstem. With regular therapy using this drug regimen, we observed a normalization of the distorted latencies of the statoacoustic pathways, followed by disappearance of the symptoms. Our explanation for this phenomenon suggests an improvement in the vestibular, ocular, and acousticocortical pathway synchronization in such older patients. We present some models.

Key Words: caloric nystagmus; dyssynchrony; prolonged latency; rotatory nystagmus; tinnitus; Vertigoheel

Neurootological patients complain of giddiness and dizziness frequently accompanied by tinnitus and hypoacusis [1–5]. These signs form the basis for a referral to a neurootologist, who should complete functional differential diagnosis and plan a lesion-oriented differential therapy.

At our Bad Kissingen neurootological research laboratory, we use electronystagmography (ENG), craniocorpography (CCG), and evoked responses. The responses, including auditory brainstem-evoked potentials, acoustic late evoked potentials, vestibular evoked brain potentials, and short-latency somatosensory-evoked potentials enable us to objectively record the responses of the statoacoustic pathways [2,6–10]. Besides using our new clinical databank (ASOAC), we employ classical threshold and suprathreshold audiometry and impedanciometry. An automatic analysis of the five-channel polygraphic ENG is processed by our system (NYDIAC) online during the performance of spontaneous and fixation, caloric, and optokinetic nystagmus. We evaluate several parameters both numerically and graphically (i.e., central nystagmus frequency, amplitude, slow-phase velocity, corneoretinal potential, and culmination latency). By means of our two-channel evoked response machine, "Bad Kissingen" type, we can easily gain numerical and graphical data of the most varied tests on the same charts. All the clinical data available are assembled in our central ASOAC computer network, which also acts as an expert system. Thus, we can quickly establish a differential diagnosis and subsequent differential therapy [2,8,10].

For many years, to obtain diagnoses we had to deal with inhibitory or overactive functional lesions obtained from peak activities of the responses, especially in equilibriometry. In addition, we also observed the existence of a time-consuming slow-reaction processing that, however, ultimately reached a normal culmination activity, especially in the vestibular calorics (butterfly chart) but also in the per- and postrotatory tests (rotatory intensity damping test) [2,6–10]. With our new evoked response techniques, we mainly check for latency prolongations [1,2].

Instantaneously, from statistics of 1,461 new patients in our ASOAC clinical databank, we selected 163

Reprint requests: Prof. Dr. C.-F. Claussen, Kurhausstrasse 12, 97688 Bad Kissingen, Germany. Phone: (+49) (0)9 71-6 48 32; Fax: (+49) (0)9 71-6 86 37; E-mail: claussensolog @t-online.de

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patients who exhibited latency prolongations at the calorics and other ENG tests and at the acoustic brainstem- and cortex-evoked potentials. We designated the patients in this group as exhibiting the slow-brainstem syndrome [1,2,11,12].

The mean age of the basic sample was 57.0 years (standard deviation [SD], 18.2 years; 89 [54.4%] female, 74 [45.6%] male). In those in the slow-brainstem group, these values amounted to a mean of 58.6 years and an SD of 18.5 years (43.0% female, 57.0% male).

As regards the subjective signs of those in the slow-brainstem group, we found vertigo in 95.7%, nausea in 59.5%, tinnitus in 57.1%, hyperacusis in 82.8%, loss of visual acuity in 65.0%, blurred vision in 10.4%, double vision in 4.9%, headaches in 17.2%, depression in 1.2%, and paresthesias in 4.3%. Basically, 30.1% suffered from a cardiac insufficiency, 14.7% from a posttraumatic state after skull trauma, 5.5% from diabetes mellitus, and the remainder from other symptoms.

Equilibriometric results showed that of those in the slow-brainstem group, 100.0% evidenced a caloric latency prolongation, 36.2% a vestibular inhibition, 5.5% a mesocephalic inhibition, 16.6% a pontine vestibular nystagmus disinhibition, 35.6% a pathological nystagmus dissociation, 37.4% a vestibular recruiting, 4.9% a vestibular decruiting, 74% a pathologically downward-beating nystagmus, 30.7% an optokinetic disinhibition; 23.9% an ataxic CCG-standing reaction, 34.4% an ataxic CCG-stepping reaction, 2.5% a CCG Parkinson pattern, and 21.5% a lateral inhibition in the CCG stepping test.

Audiometric findings revealed a prolongation of the acoustic brainstem-evoked potentials in 100.0% and of the acoustic late evoked potentials in 31.9%. Furthermore, 57.7% suffered from a cochleobasal high-tone loss, 1.2% from a cochleo-apical low-tone loss, and 19.6% from a pancochlear hearing impairment. A conductive hearing loss existed in 0.6% and a combined conductive and sensorineural loss in 4.3%. Stapedial reflex inhibitions occurred in 4.3%. The tympanogram results showed a hypermobile tympanum in 8.0% and a retracted tympanum in 11.7%. Also noteworthy is that the pure-tone audiometry readings were completely normal in 22.1% of all the slow-brainstem patients.

BASIC ASPECTS OF SLOW-BRAINSTEM SYNDROME

Much evidence supports the view that the central nervous system (CNS) is hierarchically organized. Its organization is thought to consist of a system of centers, each with the function of collecting stimuli and appropriately redispatching them [2,5].

Auditory Pathways

Ascending Pathways

The central auditory pathways extend from the medulla to the cerebral cortex. They consist of a series of nuclei (groups of nerve cell bodies in the CNS similar to a peripheral ganglion) connected by fiber tracts made up of their axons (processes that convey signals away from the cell bodies). This complex chain of nerve cells helps to process and relay auditory information, encoded in the form of nerve impulses, directly to the highest cerebral levels in the cortex of the brain [2]. To some extent, different properties of the auditory stimulus are conveyed along distinct parallel pathways. This method of transmission, employed by other sensory systems, provides a means for the CNS to analyze different properties of the single auditory stimulus, with some information processed at low levels and other information at higher levels. At lower levels of the pathway, information as to pitch, loudness, and localization of sounds is processed, and appropriate responses, such as the contraction of the intra-aural muscles, turning of the eyes and head, or movements of the body as a whole, are initiated.

In the medulla, the fibers of the cochlear nerve terminate when they reach a collection of nerve cells called the *cochlear nucleus*. The cochlear nucleus consists of several distinct cell types and is divided into the dorsal and ventral cochlear nucleus. Each cochlear nerve fiber branches at the cochlear nucleus, sending one branch to the dorsal and the other branch to the ventral cochlear nucleus [2].

Some fibers from the ventral cochlear nucleus pass across the midline to the cells of the superior olivary complex, whereas others make connection with the olivary cells of the same side. Together, these fibers form the trapezoid body. Fibers from the dorsal cochlear nucleus cross the midline and end on the cells of the nuclei of the lateral lemniscus. There they are joined by the fibers from the ventral cochlear nuclei of both sides and from the olivary complex. The lemniscus is a major tract, most of the fibers of which end in the inferior colliculus, the auditory center of the midbrain, though some fibers may bypass the colliculus and end, together with the fibers from the colliculus, at the next higher level, the medial geniculate body. From the medial geniculate body there is an orderly projection of fibers to a portion of the cortex of the temporal lobe [2,5].

In humans and other primates, the primary acoustic area in the cerebral cortex is the superior transverse temporal gyri of Heschl, a ridge in the temporal lobe, on the lower lip of the deep cleft between the temporal and parietal lobes, known as the sylvian fissure. Because about half the fibers of the auditory pathways cross the midline while others ascend on the same side of the brain, each ear is represented in both the right

and left cortices. For this reason, even when the auditory cortical area of one side is injured by trauma or stroke, binaural hearing may be little affected. Impaired hearing due to bilateral cortical injury involving both auditory areas has been reported, but it is extremely rare.

Descending Pathways

Parallel with the pathway ascending from the cochlear nuclei to the cortex is a pathway descending from the cortex to the cochlear nuclei. In both pathways, some of the fibers remain on the same side, whereas others cross the midline to the opposite side of the brain. There is also evidence of a "spur" line ascending from the dorsal cochlear nucleus to the cerebellum and another descending from the inferior colliculus to the cerebellum. The significance of these cerebral connections is not clear, but they may antedate the evolutionary development of the cerebral cortex. In general, the descending fibers may be regarded as exercising an inhibitory function by means of a sort of "negative feedback." They also may determine which ascending impulses are to be blocked and which are allowed to pass on to the higher centers of the brain [2].

From the superior olivary complex, a region in the medulla oblongata, there arises also a fiber tract called the *olivocochlear bundle*. It constitutes an efferent system, or feedback loop, by which nerve impulses thought to be inhibitory reach the hair cells. This system, which uses acetylcholine as a neurotransmitter, is presumably involved in sharpening or otherwise modifying the analysis that is made in the cochlea [2].

In cognitive simulation, computers are used to test theories about how the human mind works—for example, theories about how people recognize faces or recall memories. Cognitive simulation is already a powerful tool in both neuroscience and cognitive psychology.

The reticulospinal tracts arise from relatively large but restricted regions of the reticular formation of the pons and medulla—the same cells that project ascending processes to intralaminar thalamic nuclei and play an important role in maintaining alertness and the conscious state. The pontine reticulospinal tract arises from aggregations of cells in the pontine reticular formation, descends ipsilaterally as the largest component of the medial longitudinal fasciculus, and terminates among cells in laminae VII and VIII. Fibers of this tract exert facilitating influences on voluntary movements, muscle tone, and a variety of spinal reflexes. The medullary reticulospinal tract, originating from reticular neurons on both sides of the median raphe, descends in the ventral part of the lateral funiculus and terminates at all spinal levels on cells in laminae VII and IX. The medullary reticulospinal tract inhibits the same motor activities that are facilitated by the pontine reticulospinal tract. Both tracts receive input from regions of the motor cortex [1,2,9,10].

Information is transmitted by signals. In pure cybernetics, the physical nature of the signals is completely disregarded. Important only is that the signals can be differentiated from one another. The form of the set of possible signals and the nature of their changes are also significant. For example, a signal carrying information on the number of persons in a room cannot take on fractional values. The values of these signals change in jumps. Conversely, a signal giving information of the air temperature in a room cannot change its value, say from 19°C to 20°C, without passing through all intermediate values. Signals of the first type are called *discrete* and those of the second type *continuous*. The same terms are used in relation to the information represented by these signals.

In describing continuous information within a certain accuracy, it can always be reduced to discrete information. The usual method of representation of discrete information is as a finite sequence of signals selected from a certain fixed finite set of signals called the (*abstract*) *alphabet* (e.g., the set of letters in the Latin alphabet, the set of decimal numbers). One important but simple fact is the possibility of representing any discrete information in the form of sequences of signals of only two different types, as is done, for example, in the dots and dashes of the well-known Morse telegraph code. Problems of various forms of representation of discrete information make up the subject of a special division of theoretical cybernetics called *encoding theory*.

Increasingly, biological explanations resemble explanations in engineering, in which material structures are described and then the laws of physics and chemistry are used to explain the behavior of these structures. (In the biological case, of course, these structures are often dynamic in the sense that their molecules are continually being replaced.) Through the influence of neurophysiology and cybernetics (the science of information and control, which can be applied also to artificial automata), scientific psychology also fits well into the same mechanistic scheme [2].

Synchronizations in the data lines play an important role (Fig. 1) in establishing a typical spatiotemporal matrix for the regular flow of representations of the actual statoacoustic fields within which humans just perceive and behave. These are input cores for the higher CNS centers establishing our frame of understanding. Dyssynchronies (see Fig. 1, right) within the statoacoustic central lines then can centrally provoke alarming signals, such as vertigo or tinnitus (or both).

Ionic Basis of Electrical Signals

Ions are atoms or groups of atoms that gain an electrical charge by losing or acquiring electrons. For example, in

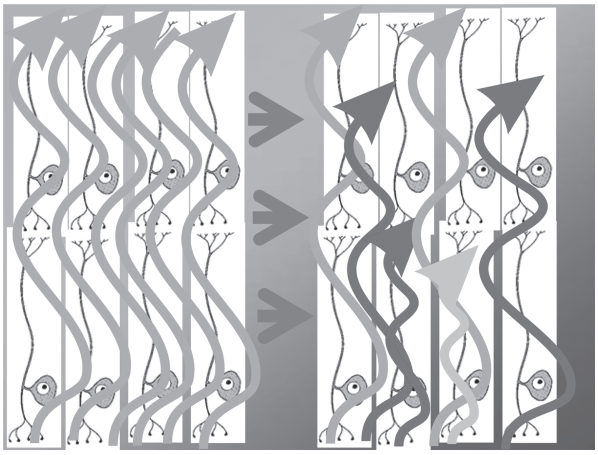

Figure 1. Model of a sensorineural central pathway with synchronized (left) and dyssynchronized (right) data transfer.

the reaction that forms salt from sodium and chlorine, each sodium atom "donates" an electron, which is negatively charged, to a chlorine atom. The result is sodium chloride (NaCl), composed of one positively charged sodium ion (Na^+) and one negatively charged chloride ion (Cl^-). A positively charged ion is called a *cation*; a negatively charged ion is called an *anion*. The number of charges carried by an ion is called its *valence*. Na^+ and Cl^-, which respectively lose and acquire one electron, have a valence of one, while calcium ions (Ca^{2+}), which lose two electrons, have a valence of two.

The electrical events that constitute signaling in the nervous system depend on the distribution of ions on either side of the nerve membrane. Underlying these distributions and their change are crucial physicochemical principles [2,10,13,14].

γ-Aminobutyric acid (GABA) and glycine are proved to cause hyperpolarization of the postsynaptic membrane. GABA is widely distributed in the brain, being especially prevalent at higher levels of the CNS [2,10, 13–15]. It is produced from glutamate by the enzyme glutamic acid decarboxylase (GAD). Consequently, the concentrations of GABA and GAD parallel each other in the nervous system.

At postsynaptic receptor sites, GABA opens chloride channels, in most cells causing a hyperpolarization of the membrane as Cl^- diffuses inward to reach its equilibrium potential. What must be pointed out, however, is that GABA inhibits presynaptic nerve fibers as well. At certain synaptic junctions, the release of a neurotransmitter is modulated by the binding to presynaptic receptors of a neurotransmitter released from other neurons. A classic example of this is at the axon terminals of incoming dorsal roots in the dorsal gray matter. Projecting onto these terminals are other terminals that release GABA. Though GABA causes an increased Cl^- conductance at these terminals, the result is depolarization, not hyperpolarization, of the membrane. This is because the resting membrane potential of the receiving nerve terminal is much more negative than the Cl^- equilibrium potential. This means that as Cl^- flows into the terminal to reach equilibrium, the membrane is actually depolarized. The effect at the terminal is a decrease in neurotransmitter release [2,10,12,14].

Unlike GABA, glycine is found mostly at lower levels of the CNS, including the spinal cord, medulla oblongata, and pons. It is a major inhibitor released by interneurons to suppress motoneuronal activity. Like GABA, glycine acts by increasing Cl^- conductance at the postsynaptic membrane, though it acts at a clearly different receptor. Apparently at least two molecules of glycine and GABA must bind to their respective receptors to activate a chloride channel. The action of both neurotransmitters is terminated by uptake back into the presynaptic terminal or into surrounding glial cells.

Histamine

The main difficulty in proving that this substance acts as a neurotransmitter is the lack of adequate techniques for identification. There is little doubt that histamine exists in the brain, but it appears to be present in at least two distinct compartments: in mast cells (nonneuronal connective tissue cells) and in nerve endings. The actions of histamine are unclear; it is reported to act as a depressor of neuronal activity at some sites and as an excitor at others [2,10,13]. However, histamine treatment is beneficial in peripheral, inner-ear statoacoustic lesions, as, for instance, in Ménière's disease, though the slow-brainstem syndrome is different from Ménière's.

THERAPY FOR SLOW-BRAINSTEM SYNDROME

In the course of neurootological examination of the geriatric population, one comes across a group of patients who exhibit a marked reduction in sensitivity of several major sensory pathways. These patients complain mostly of vertigo, with varying degrees of instability, tinnitus, and hypoacusis, and a reduced alertness state. Objectively, they exhibit an increase in latencies of both vestibular nystagmus and of brainstem-evoked potentials. These latency abnormalities suggest a diffuse affect on the brainstem transmission pathways. Such cases are considered to be affected by the condition known as *slow-brainstem syndrome*. Routinely, the clinician examines vestibuloocular nystagmus obtained from the caloric and rotatory tests for overactivity or inhibition. However, these older persons show a normal maximum intensity but a delay in peak intensity. This, combined

with an acoustic pathway delay, forms the slow-brainstem syndrome. We have noted that a combination of cocculus (picrotoxin), conium (Coniine), amber, and petroleum (Vertigoheel) has a "tune-up" effect on the brainstem in these patients. *Conium maculatum* is a tall biennial (living for 2 years) having green stems spotted with red or purple, large compound leaves, and white flowers. Coniine, the poison, is concentrated in the seeds, though the entire plant is dangerous to livestock when fresh [2, 10,11,14,16].

We postulate that diffuse degenerative metabolic changes occurring at the level of the brainstem are responsible for the slow-brainstem syndrome [14]. Possible mechanisms are hypoxia, ischemia, viscosity, and other physicochemical changes and general age-related degenerations. We postulate that parts of the neuronal networks, especially sodium and chloride channels, may be affected in some way in these patients, as deduced from the beneficial effect exerted by Vertigoheel [2,11,14].

Of general importance in this group is a holistic concept of treatment wherein the therapy is directed not only at relieving patients' neurootological complaints temporarily but at alleviating their underlying systemic illness over a sustained period. Therefore, we have designed a specific therapeutic approach to speeding up the neurootological brainstem functions pharmacologically in those with slow-brainstem syndrome [2,10,13, 14,16]. The drug, Vertigoheel, is applied three times per day sublingually in pill form.

We observe diffuse metabolic changes occurring at the level of the brainstem that appear to be to be responsible for this condition, leading to a functional dyssynchronization within the statoacoustic pathways, appearing also as an age-dependent process. We postulate that parts of the neuronal networks, especially sodium and chloride channels, may be affected in some way in these patients, as deduced from the beneficial effect exerted by Vertigoheel.

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