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Dorsal Root Ganglia may be Reservoirs of Viral Infection in Multiple Sclerosis

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Abstract—There are presently two competitive theories that attempt to explain the etiology of multiple sclerosis (MS). Briefly summarized, they are: 1. An *infection*, probably of viral type, may attack the oligodendroglia of the central nervous system; or, 2. An *autoimmune* process may begin with an infection of the peripheral lymphatic immune system, producing antibodies that cross the blood-brain barrier, leading to myelinoclasia. Since 1935, research has been directed toward myelin of the central nervous system and the myelin sheaths of peripheral nerve; however, dorsal root and cranial sensory ganglia (DRG) have apparently not been studied. The present hypothesis states that an infectious agent (probably viral) finds privileged sanctuary in the dorsal root and cranial sensory ganglia (DRG): thereafter periodically invading the spinal cord, brain, or peripheral nerve. Previously reported erratic spinal fluid viral titers and cultures can be explained by differences in the anatomy of the DRG in which there is a variable and limited contact of spinal fluid with sensory ganglia. Clues to this hypothesis were noted by the author during routine neurological examinations of patients with MS, in which sensory signs and symptoms were frequently encountered. This clinical observation has also been reported by others who found such symptoms in 75% of MS patients, ranking second only to incoordination.

Multiple sclerosis (MS) is widespread, having a worldwide frequency of over 2 000 000 patients. Its incidence in the United States is approximately 60/100 000 in the Northeast, increasing northward into Nova Scotia, and then climbing even further to a remarkable 150/100 000 in the Shetland and Orkney Isles off northern Scotland. This unexplained latitudinal phenomenon was first described by Kurtzke (1) who reported that the disease occurred twice as often above and below 37°parallels as between them. He and numerous other researchers hypothesized that an infection is responsible, probably a virus or viruses, endemic to temporate regions, affecting large numbers of individuals before puberty. In addition, several clusters of patients were reported from certain low frequency geographic areas; apparently strengthening the infectious theory. But in a recent review, Poser (2) reviewed the above postulates, and concluded that Kurtzke's (1) theory was flawed, stating that strong genetic traits of susceptible populations (inherited from ancient Viking explorers) were underestimated, and that infections as well as vaccinations

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early in life could be the inciting events of the '*MS trait*'. Added to ongoing scientific disagreements concerning latitude and genetics, two older more all-inclusive theories that began in 1935 will be reviewed: the *autoimmune* versus the *infectious*.

The dorsal root ganglion (DRG) hypothesis

This present article adheres to the infectious theory, as follows: 1. Virus or viruses in the active phase periodically invade the central or peripheral nervous system from various peripheral sensory ganglia (DRG) or sympathetic chain where viruses can exist for many years in the latent phase. 2. Demyelination follows an infection of oligodendroglial cells, possibly from one of the coronaviruses (3). 3. Exacerbations in MS occur because of virus activation in DRG (4), or from immune cross-reactions between similar viral peptide sequences and myelin basic protein (5), or from vasculomyelinopathy produced by virus particles that invade endothelial cells (6). In summary: *infection of oligodendroglia or endothelial cells emanates periodically from the DRG reservoirs, and myelinoclasia occurs from several mechanisms.*

On first inspection this hypothesis seems untenable, because dorsal root and cranial sensory ganglia are part of peripheral nerve, whereas almost all research since 1935 has been concentrated on the spinal cord, brain, and on nerve. Poser (7) reviewed the literature concerning peripheral nerve lesions in MS patients, concluding the lesions were secondary to autoimmune mechanisms. No mention was made of the pathophysiology of DRG.

Sensory manifestations of MS have been known to neurologists from the time they were first described in 1872 by Charcot (8). 75% of patient examinations will yield puzzling sensory signs that suggest some type of involvement somewhere in the sensory system, and rank second to posterior column and cerebellar signs (7–17). Sensory symptoms herald the first attack in more than 30% of patients, and another 30% will develop pain during the illness (11). Moulin, Foley, and Ebers (14) found that 55% of MS patients developed pain that was classified as stereotyped paroxysmal pain in 24%, and acute paroxysmal pain (such as trigmeminal neuralgia) in 9%. Recently, Stenager et al (16) reported acute and chronic pain in 117 patients with MS, in whom 23% had pain at onset. Radicular pain was the first sign of MS in 11 patients studied by Ramirez-Lassepas et al (17), in which only 2 of 5 magnetic resonance imaging studies (MRI) revealed plaques in pain pathways. Bilateral tic douloureux in young women is a recognised symptom of MS, and may be the only pathognomonic sign of MS. Proven sites of these high intensity jabs of pain are unknown, though lesions of root entry zone and descending sensory pathway of cranial nerve V are mentioned in most articles as etiology. However, white matter lesions of the pons or medulla are rarely demonstrated in patients with tic-like pain by magnetic resonance imaging (MRI) or at autopsy, strenthening the possibility that the pathology of trigeminal and glossopharyngeal neuralgia in MS may lie in certain cranial ganglia.

Numerous signs and symptoms suggesting DRG or peripheral nerve involvement have been noted by the author over 36 years experience in practice, in 2 large clinics for MS patients, and in research. These are: typical nerve root pain over the trunk, various neuralgias that seem to be of plexus origin (most often in the arms), patches of sensory loss of paresthesiae (of oblong configuration on the extremities), girdle pains, deep pain in the pelvis or lumbar spine, and absent deep tendon reflexes (DTRs), usually in the legs. These absent reflexes are puzzling and not well understood, being explained in some textbooks as cerebellar in origin. This is untenable because cerebellar lesions result in DTRs that are depressed, not absent. Interruption of the reflex arc, possibily in the sensory limb, is a more likely explanation.

Peripheral myelin, central myelin, and DRG

Central nervous system myelin differs from peripheral nerve myelin in its embryologic development. At the strategic interface of these two types of myelin lie the DRG that can be thought of as the 'borderland of the nervous system' because of certain embryological, anatomical, and physiological concepts; particularly because of the bipartite embryological origin of DRG (18). These are formed during fetal development, partly from cellular migrations of neuroblasts from the neural crest adjacent to the neural groove, and partly from primitive ectoderm. Dorsal root ganglia migrate into the spinal foramina, where peripheral nerve begins. Glioblasts from near the neural crest contribute the Schwann cells that originate in the sensory root and migrate distally, producing myelin of peripheral nerve, contrasted with oligodendrocytes of spongioblast origin that migrate centrally and produce myelin of the cord and brain.

Sensory ganglia of cranial nerves have opposite origins compared with DRG. Epibranchial placodes of epidermal origin are located along the side of the head of the embryo from where they migrate inward, compared with dorsal root ganglia that migrate outward. The sensory ganglia of cranial nerves V, VII, VIII, IX and X are formed in that manner (19). Therefore, DRG bear a closer relationship to neurons of the neuraxis than to peripheral nerves. In addition, some

of the ganglia are bathed by variable amounts of cerebrospinal fluid. This is because of lateral extensions of some root sleeves, because of subarachnoid pathways in Meckel's cave, and because of Tarlov cysts in the sacral segments (20, 21). This may explain sporadic positive viral cultures and antibody levels reported by some workers as probable etiology of MS. In addition, viruses in DRG during their latent phases may produce little antibody.

Demyelinating plaques of spinal cord and brain can often be demonstrated in asymptomatic individuals at autopsy and by magnetic resonance imaging (MRI): in addition, plaques in patients with MS usually far outnumber the neurological signs produced by them. This was actually proven two decades ago by the neuropathological studies of MacKay and Hirano (22), who found in 1967 that 20% of autopsied study groups never experienced signs or symptoms of MS, even though significant numbers of plaques were found at autopsy. Further confirmation came from MRI diagnostic studies in MS over the last 5 years, during which neurologists studied monosymptomatic patients who often had 30–60 demyelinating plaques on imaging studies. These observations suggest that the putative organism(s) of MS is a common infectious agent(s), infecting many asymptomatic individuals, and is an infection that is well tolerated by most.

Myelin of peripheral nerve is produced by Schwann cells that originate in the dorsal root, contrasted with the oligodendroglia of cord and brain that produce central myelin. There are now over 40 publications concerning peripheral nerve lesions in MS describing myelin produced by the Schwann cells, thus challenging classical teachings that MS affects only the central nervous system. Poser's (7) scholarly review of patients with peripheral nerve lesions described subtle signs of damage in sural nerve biopsies, examined by electron microscopy, and Sedgwick (23) described alterations in 84% of cervical somatosensory evoked potentials in MS. The numerous peripheral nerve lesions described by Poser (7) might represent either portals of entry of viral infection, or perhipheral spread of disease from DRG.

Autoimmune and infectious theories—scientific controversies

Experimental allergic encephalomyelitis (EAE) was first produced by Rivers and Schwentker (24) in 1935, followed by numerous confirmations (25) including a relapsing type (26). Thus, the stage was set for hundreds of more recent articles devoted to the now popular *autoimmune* theory. Shortly after EAE was described, a second historical discovery was made in which it was found that slow viruses can lie latent with incubation periods of more than 10 years. The first such infection described was scrapie, identified in 1936 by veterinarians Cuille and Chelle by transmission to sheep: confirmed in 1960 by transmission to other species (27). Between 1965–1971, the following human slow viruses and proteinaceous infectious particles (PRIONS) were identified: subacute sclerosing panencephalitis, progressive multifocal leukoencephalopathy, progressive rubella encephalitis, persistent immunodeficiency infection, kuru, Creutzfeldt-Jakob disease, and Gerstmann-Strauller-Scheinker disease (27, 28). Discoveries of EAE and slow virus identification followed so closely upon one another that it seemed that the enigma of MS would soon be solved, but the predictions were too sanguine.

The autoimmune theory

This now popular theory states that the lymphatic immune system is primarily infected, myelinoclasia resulting from an attack on myelin or glia by immune complexes of peripheral origin that cross the blood-brain barrier. Viruses that can infect lymphoid cells in human autoimmune diseases are: influenza, measles, mumps, rubella, vaccinia, and varicella (29, 30). Today's two controversial theories have both included measles and rabies as important concepts in explaining each proposition (see below). Measles is particularly interesting to researchers as the putative inciting event, because its antibody levels were elevated in MS in 31 of 35 surveys (10, 31). Johnson et al (29) and Gendelman et al (30) (using measles only as a paradigm), concluded that measles encephalomyelitis is probably secondary to an infection of the somatic lymphatic immune system with secondary autoimmune damage to myelin, citing evidence that spinal fluid cultures in measles encephalomyelitis were negative, and spinal fluid anti-measles antibodies were erratic. Further proof of autoimmune mechanisms were positive lymphoproliferative responses to myelin basic protein in patients with several types of viral encephalomyelitis, particularly measles, as well in rabies postvacinnal reactions.

The infectious theory

This competitive theory holds that there is a primary central nervous system infection of the oligodendrocytes or other susceptible tissue that precedes myelinoclasia. No virus has thus far been proven, although a disconcerting number have been identified in MS: measles, caprine arthritis encephalitis, Epstein Barr, herpes simplex, human immunodeficiency virus-1, human T-cell leukemia virus I and II, in-

fluenza C, mumps, parainfluenza III, rubella, vaccinia, varicella-zoster, and coronavirus (3, 10, 27, 31–39). Five reports of positive measles virus isolation in measles encephalomyelitis (32–37) have challenged the infectious theory. Neuroscientists await confirmation of the recent work by Murray et al (3) who discovered coronavirus RNA and antigen in brain of 12 of 22 autopsied cases of patients with MS. If true, it might unravel the mystery of the many plaques in asymptomatic individuals who live in cool climates. Thus, the infectious agent of MS could be a common one: perhaps even the common cold.

It is interesting that rhabdoviruses in Russia have been recovered from a number of patients, but this startling finding has not been confirmed by other laboratories (27, 32). Rabies virus studies have long played an important part in MS research because: 1. Long incubation periods in rabies span the theoretical 10 to 15 year incubation of MS (40). 2. Rabies virus lies protected in neurons for long periods where no antibody response can be mounted, and where antibodies cannot attack (41). 3. Sensory neurons are the conduits used by rabies virus during centripetal spread into DRG, where the first replication occurs (42).

There are now two case studies (43, 44) of acute rabies associated with extensive perivenular demyelination that question the conclusion by autoimmune theorists that rabies postvaccinal reactions are due exclusively to immune processes. The coexistence of acute rabies accompanied by widespread demyelination was first published by Toro, Vergara, and Roman (43) in 1977 who studied neuroparalytic accidents following rabies vaccination in 21 cases. They described the neuropathology of a boy (case 18) who died after being bitten by a dog. On the 14th day of vaccination, he showed complex neurological signs thought to be postvaccinal disease. At autopsy, acute rabies was diagnosed serologically, by culture, and from the presence of Negri bodies: along with extensive perivenous demyelination. Nelson and Berry (44) reported a woman who had been bitten on her thumb by a bat, given proper postexposure prophylaxis and also misdiagnosed as postvaccinal encephalomyelitis; however, her autopsy revealed advanced demyelination in the cervical spinal cord, where rabies apparently invaded through her cervical sensory roots.

Tangchai and Vejjajiva (42) in rabies autopsy studies, described DRG that contained coarse basophilic granules in the cytoplasm, and dark round bodies in the nuclei. Others identified changes in the capsular cells (41). Neuropathology of peripheral nerve and DRG in measles were identified in subacute sclerosing panencephalitis by Radermecker (45), and measles inclusion bodies were identified in the ganglion cells of the retina in 1970 by Nelson et al (46).

Research tools to investigate the DRG hypothesis

The exact research tools with which to study the DRG hypothesis are speculative; however laboratory reproduction of sensory signs and viral studies of DRG can be mentioned. Neurological signs in MS can be reproduced in the laboratory by induced hyperthermia testing (47–49). A newer, safer version of the test is now being used (50) because of complications from hot water immersion studies (51). Croen et al (4), and Mahalingam et al (52), by the use of in situ hybridization to labelled RNA probes; studied HSV-1 in trigeminal ganglia recovered at autopsy from 47 subjects. The virus was identified in 67%, equal to the national incidence of seropositive adults. Latent HSV-1 was found in 87% of trigeminal ganglia compared with 53% of thoracic ganglia. Latent HSV virus has now been identified in central nervous systems, in dorsal root ganglia, and in autonomic ganglia.

Comments

There are actually close interrelations between the infectious and the autoimmune theories: however, in both, an infection is thought to be the primary event. An initial infection of oligodendroglial cells may be primary, accompanied by immune-related events in adjacent cells that produce vasculomyelinopathy by the invasion of virus into the endothelial cells of vessels of the central nervous system. Poser's (6) recent review of subacute sclerosing panencephalitis SSPE clearly described that mechanism, but he did not relate it to MS etiology. Equally plausible is the proposition that demyelination can be produced by viral specific amino acid antigenic sequences (epitopes) that unite directly with homologous target decapeptides in myelin of brain, cord, and peripheral nerve (without an infection of the lymphatic immune system), proposed by Jahnke, Fischer, and Alvord (5). Thus, neuroscientists have promulgated three separate theories in which *infection* inside the neuraxis is the primary event: 1. Direct infection of oligodendroglia, 2. Viral epitopes that attack formed myelin, and 3. Vasculomyelinopathy from viral antigen in endothelium. The DRG hypothesis maintains that viruses might migrate in and out central and peripheral nervous systems from strategically placed safe haven reservoirs in the cranial sensory and dorsal root ganglia.

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