Behavioral Consequences of Infections of the Central Nervous System: With Emphasis on Viral Infections

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Infections of the central nervous system can damage the brain and cause abnormal behavior. In this article, the authors examine how behavior is affected by damage to different parts of the brain. They then focus on damage caused by specific infections of the brain and how these can result in abnormal behavior with legal consequences. Examples of such infections include neurosyphilis, encephalitis lethargica, herpes simplex encephalitis, and various other viral encephalitides, both acute and chronic. The AIDS dementia complex, which results from HIV infection of the brain, causes behavioral abnormalities in addition to motor and cognitive impairments. In some cases of violence and other criminal behavior, this can be a consequence of central nervous system infection, and the authors suggest that criminal sanctions in such events are inappropriate in the absence of volitional criminal intent.

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Infections of the nervous system can damage areas of the brain responsible for the regulation of behavior and can result in abnormal, inappropriate behavior that can get the affected individual in trouble with the law. The behavior can occur as part of the acute illness or part of a chronic progressive disease course, or it may be the residual effect of damage to the brain caused by the acute illness. There are other types of legal ramifications of nervous system infections, such as difficulties with memory and executive function, which may render otherwise normal-appearing persons unable to continue with their accustomed occupations and lifestyles. Examples of each follow in the body of this review.

Damage to the brain can affect adversely many aspects of human function. Apart from localized deficits, such as arm or leg weakness and numbness, loss of vision, unsteadiness of gait, loss of bladder and bowel control, the higher functions, including memory, ability to concentrate, plan, understand the consequences of one's actions, and control impulses, are often also adversely affected. Very small lesions in silent areas of the brain may have no easily discernible effect on an individual's ability to function. Larger, more diffuse or multiple lesions, however, usually are clinically manifest, even to the casual observer. Some of these manifestations prevent normal integration into society and a very few result in antisocial and even criminal behavior.

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A Famous Case History

Such brain lesions can be due to a multitude of causes such as stroke, infection, or trauma. The oft-repeated case of Phineas Gage illustrates this point well.[1–3]

> Phineas Gage, a young foreman on a railroad construction crew in New Hampshire, while unschooled, was said to have had a "well-balanced mind [and] was very energetic and persistent in executing all his plans and operations." On his job, Gage used a pointed iron bar (three feet seven inches long, one and one quarter inches at its widest point) to tamp blasting powder into a narrow hole. One day, a spark ignited the powder, and the tamping rod was propelled directly upward, entering Gage's head in the left maxillary area and protruding through the top of

his skull. Though unconscious for a short time at the accident site, he regained consciousness before arriving in the nearest community for medical attention. There the tamping iron was removed and, to everyone's surprise, Gage not only survived but was free of neurological disability such as paralysis, sensory loss, and visual field disturbance.

A striking alteration in Gage's personality was soon obvious, however. He had been a God-fearing, family-loving, teetotaling, and scrupulously honest working man, but his behavior changed so dramatically that his workmates said he was "no longer Gage." Harlow eloquently described this post accident behavior:

"The equilibrium or balance, so to speak, between his intellectual faculties and animal propensities seems to have been destroyed. He is fitful, irreverent, indulging at times in the grossest profanity, manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of operation, which are no sooner arranged than they are abandoned in turn for others appearing more feasible. A child in his intellectual capacity and manifestations, he has the animal passions of a strong man. . ." [Ref. 1, p 211].

This type of behavioral alteration has also been described after viral and other infections of the central nervous system, in which particular areas of the brain are damaged. We devote this article to the description and characterization of such abnormal behavior.

Early Case Histories of Viral Infection

In the earlier parts of the 20th century, when certain infections of the central nervous system, such as von Economo's encephalitis and untreated neurosyphilis, were more common, the adverse behavioral consequences were well known, though not necessarily well understood. The epidemic of von Economo's encephalitis in the second and third decades of that century clearly demonstrated that an encephalitis with prominent brainstem involvement could result in antisocial behavior, with legal consequences, as a residual effect.[4] The adverse effects of neurosyphilis on behavior were familiar in the era before penicillin, and the resulting impulsive grandiose illegal acts were a well-known consequence of the disease. An example of violent abnormal behavior during an infection of the brain is the following narrative of a probable case of viral encephalitis:

The patient, a 27-year-old divorcee, was reportedly under great stress in a new job beyond her abilities. She developed a sense of malaise and diarrhea. She then was unable to sleep and lost her appetite. Her memory was gone and she was uninterested in life. She heard music that others could not hear. On admission she was immobile. Described as showing a "flattened affect with ludic overtones," she had occasional episodes of screaming and shouting. Spinal tap showed 62 lymphocytes, 5 polymorphs with protein of 51 mg %. EEG was normal. She reported seeing insects and other animals crawling on her bed. She referred frequently to wishing that she was dead and that someone would kill her. On one occasion she attempted to strangle herself and her nurse with a bell cord. She required heavy sedation for control. The temperature was at first normal but within the first week became elevated, rising as high as 106°F. There was gradual improvement and she was discharged as asymptomatic ten weeks after onset [Ref. 5, p 75].

In some cases, viral encephalitis can cause premorbid personal idiosyncrasies to be so exaggerated as to lead to possible civil complaints:

The patient was a 17-year-old girl with a history of poor schoolwork with sexual promiscuity. She threatened to have a nervous breakdown if her boyfriend left her. Shortly after, she had a generalized headache and fever up to 102. This cleared but her behavior became more abnormal in the sexual area. She suggested performing sexually perverted acts with her boyfriend and her uncle. She masturbated openly. Her speech became "drawling" and there was some clumsiness of her gait. She ate with her fingers. She was incontinent and unconcerned about it. An initial spinal tap was said to be normal and she was given an electro-convulsive treatment on the basis of the diagnosis of schizophrenia.

She became sleepy and was then hospitalized at The Mount Sinai Hospital. On the admission examination she was uncooperative. She grimaced and masturbated. Despite the presence of an inconstant left Babinski it was felt that her behavior could be due to "schizophrenia." Intravenous sodium amytal did not make her more communicative. Spinal fluid showed 96 leukocytes per cubic millimeter, 95 percent lymphocytes and protein 34 mg %. Electroencephalogram was obscured by artifact. Neurologic signs including convulsions, dyskinesias, and oculogyric crises developed. Temperature rose as high as 107 before gradually diminishing. There was slow improvement in her language but she continued to show episodic rage and used obscene language. She was discharged after three months requiring later admission to a state mental hospital before being discharged as asymptomatic [Ref. 5, p 74].

Neurological Manifestations of Bacterial Infection

However, not all infectious cases of acute onset of inappropriate behavior are due to viruses. Some are due to bacteria. An illustrative example of aggressive behavior leading to trouble with the law was due to *Bartonella henselae*, the causative organism of cat-scratch disease (CSD):

A 27-year-old man presented. . .with a chief complaint of confusion and aggressive behavior of several hours' duration. He was brought to the emergency department by police in response to a call from the patient's wife. According to the wife, he had

> been terminated from his job as a truck driver 2 days before admission because of personality changes and aggressive behavior presumed to be due to drug abuse. The patient had experienced fever to 40°C, swollen nodes and a 6 pound weight loss over the past 6 weeks. . . . A complete neurological examination showed the patient's inability to recognize familiar faces. At times, he became very combative. . . . An EEG showed nonspecific diffuse slowing consistent with encephalitis. . . . A drug screen was negative for drugs of abuse. . . . A biopsy of the right inguinal node showed follicular hyperplasia consistent with cat scratch disease [Ref. 6, p 52].

Such combativeness during the acute illness is well documented in CSD. In one study, a review of the records of 3,000 cases of CSD uncovered neurological complications in 76 of them and encephalopathy with confusion and seizures in 61 of those cases. In 24 of those 61 patients, transient combative behavior occurred, especially postictally, with "hitting, pushing away, and vocally protesting," which appeared to be provoked by touching the patient "around the head or neck."[7]

Therefore, in cases of uncharacteristic criminal behavior by those with no previous history of trouble with the law, the possibility of the effects of an intercurrent infection of the central nervous system must be considered. This is especially the case when the behavior is accompanied by a fever or seizures of recent onset, neurologic abnormalities, or abnormal test results on neuroimaging, electroencephalogram, or cerebral spinal fluid assay.

That viral infections of the brain cause abnormal and violent behavior is well established in animals. For example, rats inoculated intracerebrally with Borna disease virus, an RNA virus, exhibit behavioral abnormalities in which they show abnormal alertness that progresses to violence directed toward their cagemates.[8] One of the hallmarks of rabies is a change in behavior of the infected animal. For example, a timid animal may become aggressive.[9] One of the most dramatic scenes in literature portraying a rabid animal occurs in Harper Lee's *To Kill A Mockingbird*.[10] There are many other examples of viral infections of the brain causing abnormal behavior in animals, such as hyperactivity, hypoactivity, and learning disabilities in mice recovering from herpes simplex virus infection, decreased locomotor activity in mice chronically infected with lymphocytic choriomeningitis virus, and hyperexcitation in mice infected with a neurotropic strain of rubella virus.[11]

Brain Structures of Functional Importance

While the structural correlates of various types of behavior are only partially known and understood, several discrete syndromes are well known and correlated with damage to discrete areas of the brain. These correlations have been observed empirically in patients with head injuries (such as Phineas Gage) as well as in patients with strokes. It is important to be aware that the consequences of damage to a particular part of the brain distorts the function, not only of that part, but also of all other structures connected to that part. Because the brain is widely interconnected, the localization of function and of function-structure relationships is complex, and damage to different parts of the brain can produce similar clinical pictures.

It may be useful for our purposes to think of the brain as consisting of a modern neocortical part imposed on a "corebrain," the latter consisting of upper brainstem structures and parts of the forebrain or cerebrum.[9] This corebrain, especially the diencephalon, is responsible for many of the housekeeping functions of the body, regulating appetite, body temperature, and reproduction and hormonal balance as well as the behavior that achieves these, including "fight or flight." The behavioral functions of the corebrain are modulated by the neocortex, and damage to them can induce inappropriate behavior, some of which results in violence.[9] Damage to the corebrain or the parts of the brain that modulate it, can result in violent (or other abnormal) behavior.

The frontal lobes mediate many of the most important functions of behavior, in part by modulating the corebrain. The anterior frontal lobes are responsible for appropriate social behavior, with the characteristic modulation of behavior that constitutes personality and with planning and foresight of the consequences of behavior. Damage to the anterior frontal lobes results in several characteristic behavioral syndromes.

The more posterior parts of the frontal lobes are concerned with motor function, its initiation and execution and sensory reception and integration. For the proper movement to be made, the frontal lobes act in concert with the basal ganglia, which control the proper tone in the muscles, and the cerebellum, which controls the postural adjustments necessary to execute smooth and precise movements. Thus, dam-

age to the basal ganglia results in rigidity and resting tremor, and damage to the cerebellum results in a jerky decomposition of movement, especially when very fine movements, such as writing, are to be smoothly executed.

The temporal lobes are concerned with hearing, smell, and memory. The anterior temporal lobe, containing the hippocampal complex and uncus, is integral to the sense of smell and to memory. The posterior temporal lobes contain the apparatus necessary for ability to receive language. The temporal lobes also form part of the limbic system.

The limbic system, which partly overlaps the temporal lobes, consists of the amygdala, hippocampus, septum, cingulate gyrus, cingulate cortex, hypothalamus, mamillary bodies, and fornix and plays a central role in the regulation of emotion. The hypothalamus is a gray matter structure that is embedded deep in the central parts of the brain and governs vegetative functions, such as regulation of temperature, appetite, emotion, and sexual drive, and the behavior that mediates these functions.

The parietal lobes mediate perception of spatial relationships and orientation. In particular, they integrate information from different sensory modalities, such as touch, joint position sense, vision, and hearing, to orient the body in space and to orient parts of the body to each other. The parietal lobes also properly position one's surroundings and mediate the correct perception of the position, size, shape, and texture of surrounding objects and their position in space.

Behavioral Correlates of Focal Brain Lesions

Damage to the frontal lobes induces several different syndromes, which are well illustrated in the vignette about Phineas Gage. Such patients often become impulsive, with socially inappropriate behavior that is heedless of the consequences. Their behavior is disorganized. They lack ability to plan ahead and are easily frustrated when they are unable to achieve goals, occasionally becoming violently enraged at trivial slights and setbacks. This has been called the pseudopsychopathic frontal lobe syndrome and is characteristic of damage to the orbital and dorsolateral frontal regions. Other patients exhibit abnormal placidity and lack of drive. They speak little and lack spontaneity of behavior. They answer questions correctly, but slowly, and with a significant delay in responding. Extensive lesions in the frontal lobes bilaterally may lead to a state of akinetic mutism, in which the patient may not speak or even move for days or weeks. This has been labeled the pseudodepressed frontal lobe syndrome and is associated with damage to the sagittal, medial dorsal, and medial polar aspects of the anterior frontal lobes (Ref. 1, p 113).

Damage to the limbic system, particularly the temporal lobes, results most prominently in difficulties in understanding and deciphering spoken language and in faulty memory and poor recall of recent information (Ref. 1, pp 170–2, 195). Aberrant function of this area can also cause auditory hallucinations, some of which can have considerable structure. These can resemble the state of delirium tremens, which occurs during alcohol withdrawal. Damage to parts of the limbic system occurs particularly in the Korsakoff syndrome of alcoholism and in association with herpes encephalitis, which specifically tends to damage the anterior temporal lobes (Ref. 1, pp 185–7). Lesions in the hypothalamic area can result in rage reactions to relatively trivial stimuli.

Damage to the parietal lobes causes distortion of perception of spatial relationships. One of the simplest deficits is that of inability to identify correctly a number drawn on a hand (astereognosis). Another well-known deficit is spatial neglect, which is seen in patients with a stroke in the right parietal lobe, in which the patient denies that his left arm, when raised up and shown to him, is his. Dressing apraxia, a manifestation of damage to the parietal lobes, distorts one's sense of the shape and spatial orientation of clothes, and renders the patient unable to dress himself. Objects in space may be perceived as having distorted shapes and sizes (metamorphopsia) as can be seen in the "Alice-in-Wonderland syndrome," associated with Epstein-Barr virus (EBV) infection. These misperceptions may be met with indifference or considerable anxiety, depending on the circumstances of the damage.

General Remarks on Central Nervous System Infections

Infections of the central nervous system may affect the brain focally, diffusely, or multifocally. In general, most forms of viral encephalitis present with headache, fever, drowsiness, delirium, and variably with seizures, poor memory, hallucinations, tremors, and weakness in the extremities. Many begin focally, and some parts of the nervous system are particularly susceptible to infection (and damage) by particular

viruses (Ref. 12, p 37, and Ref. 13). Thus, herpes encephalitis usually begins in the temporal and frontal lobes, giving rise to the characteristic behavioral abnormalities seen in this disease. Other viral illnesses, such as enterovirus 71, may preferentially affect the brainstem. Rabies virus seems to infect the brain widely, but it affects different groups of neurons differently, with the core areas of the brain, which modulate behavior, particularly damaged.[9,11] The long-term effects of the disease may reflect structural damage. Thus, a viral infection that damages motor neurons in the spinal cord (e.g., poliomyelitis) causes paralysis of those muscles supplied by the affected parts of the cord. Damage to the temporal lobe structures mediating memory and recall, a typical result of herpes simplex encephalitis, can result in severe, disabling memory loss. Antonio Damasio has recorded a rather poignant illustration of this type of residual disability, and described such a patient as follows:

> David, who has one of the most severe defects in learning and memory ever recorded, cannot learn any new fact at all. For instance, he cannot learn any new physical appearance or sound or place or word. As a consequence, he cannot learn to recognize any new person, from the face, from the voice, or from the name, nor can he remember anything whatsoever regarding where he has met a certain person or the events that transpired between him and that person. David's problem is caused by extensive damage to both temporal lobes, which includes damage to a region known as the hippocampus (whose integrity is necessary to create memories for new facts) and the region known as the amygdala (a subcortical grouping of nuclei concerned with emotion that I will mention in the pages ahead). . . . David's memory was entirely normal until the day he was struck by a severe encephalitis. In David's case, this infectious disease of the brain was caused by a virus, the herpes simplex virus type 1 [Ref. 14, p 115].

Behavioral Residuals of Central Nervous System Infections

Syphilis

Known since the 1400s, syphilis is a classic central nervous system (CNS) infection that specifically alters behavior and personality. The disease is caused by the bacterium *Treponema pallidum*, which is transmitted sexually. The course of the disease is divided into primary, secondary, and tertiary stages. The primary stage is a local infection at the site of transmission, usually the genitalia, and is characterized by a painless ulcer, the chancre, which appears within a few days to weeks of initial deposition of the bacteria. This is followed, after a three- to six-week symptom-free period, by the secondary stage, characterized by nonspecific symptoms, such as headache, fever, joint pain, loss of appetite, sore throat, and a generalized rash. These symptoms generally resolve in 3 to 12 weeks without treatment and are followed by an asymptomatic phase known as latent syphilis. In about one-third of infections, the disease progresses several years to decades later to tertiary syphilis, in which specific organs, one of which is the brain, begin to show damage from the long-standing infection. There are two basic forms of tertiary neurosyphilis: tabes dorsalis, which affects mainly the spinal cord and spinal nerves, and paretic neurosyphilis, which is relevant to our discussion. In any patient, both forms may be present, and the resulting condition is known as taboparesis. Usually, one form predominates.

Paretic neurosyphilis, also known as general paresis of the insane, is a chronic inflammatory condition of the frontal and temporal cortex. It causes diffuse damage and can be divided into several stages.[15] It is because of the prominent and troublesome personality changes that the first stage has been called the "medicolegal period" by Merritt *et al.*[15] This first stage may be of sudden or gradual onset and is characterized by poor judgment, impulsivity, and emotional instability, illustrating frontal lobe damage. The following cases were described by Merritt *et al.* and illustrate the point:

> [Case 1.] J.M. was a millworker, aged 49, who was brought to the hospital by his family because of his queer behavior. He had been well and working regularly until the onset of his illness. He drank moderately, being known as a "Saturday night drinker." Nevertheless he had been industrious and supported his family. About 6 months before entry to hospital he began to have headaches, was nervous and slept poorly. Then he became apprehensive over the future of his children and often talked rather incoherently on this topic. His employer reprimanded him for being late and neglecting his work. On one occasion, he arrived for work several hours too soon. His conversation became foolish and he could not be entrusted with simple errands. Lately he had taken to running away and hiding in bushes along the roadside. On one such occasion he had been apprehended by the police.
>
> [Case 2.] The wife and sister of one of our patients insisted that he left home the morning of his hospital admission showing nothing suggestive of mental disorder. As he walked to his place of employment where he was a clerk on a salary of $20 a week, he stopped to order 2 Rolls Royce cars, insisting that he was a multimillionaire and had a monopoly on the world's coffee market. From that moment he had delusions of grandeur and was excited.

[Case 3.] A schoolteacher drove to the school supply yard and loaded lumber on his car, which he took home intending to build some chicken coops. An associate, seeing him do this, telephoned his wife, who easily persuaded him to return the stolen lumber, not because he was aware of committing theft, but because he was easily influenced. Only then did the family, recalling numerous oddities of behavior over months, realize that he needed medical treatment.

[Case 4.] Another man on leaving a theater with his wife grabbed a handbag from an unknown woman and ran down the street until being apprehended by the police. His state was such that the officer had no doubt that he was in need of hospital care.

[Case 5.] A patient was brought into the hospital during the night by the police because he had run amuck [*sic*] at his rooming house, breaking up the furniture and shouting loudly. After breakfast, he was quiet, cooperative, and showed no evidence of mental disturbance. Not until many days later did another outbreak occur, following which there was evidence of mental deterioration [Ref. 15, pp 197–200].

It is evident that in such patients, the damage to the frontal lobe leads to aberrant behavior that may have legal implications. These patients are unaware of the impropriety of their behavior, and they are most appropriately handled medically rather than punitively.

Encephalitis Lethargica

Encephalitis lethargica is an encephalitis that was pandemic from 1915 to 1925. The exact cause is unknown, but it is believed to be a viral infection. It affects the brainstem and central gray structures, including the midbrain and hypothalamus.[16] For unknown reasons, the epidemic disease disappeared in the late 1920s. The epidemic occurred before modern virological methods were developed, and for that reason the cause remains unknown. However, the residual effects on behavior became well known during and after the epidemic, and some patients with no previous history of behavioral problems got into trouble with the law. It was noted that children were especially affected:

. . .In many cases there was much more than this. The children become aggressive, quarrelsome, and cruel, show morbid sexual tendencies, and steal, while in some cases they become suicidal or even homicidal. Such cases are quite beyond parental control, and the question of how to deal with them becomes a medicolegal problem of considerable difficulty.

[Case 1.] One of my cases, a boy of 16, for whom some suitable work was found was dismissed on the following grounds: He was sharp and could work quite well if watched; otherwise he would wander around, pilfer small articles, annoy the others, and be somewhat unpleasantly amorous toward those of the opposite sex. He would also go round and lick the plates of the others after dinner. This boy previous to his illness had for some time taken a high place at school.

[Case 2.] [There was] a boy who "took up a knife to his mother," "threatened to cut his brother up," and "took a hatchet to his sister." Eventually it was necessary to send him to an asylum. In the asylum he was quarrelsome and aggressive, but mentally alert and active, and very difficult in consequence.

[Case 3.] [There was] the case of a young woman whom it had been necessary to send twice to an asylum. Previous to a typical attack of encephalitis she had been an exceedingly amiable and invaluable help to her mother in their household. Since the attack her behavior has broken up the peace of the family. She is a big, powerful girl, and in addition to periodic outbursts of violence toward her parents if crossed in the smallest matter, she has made mischief with the neighbors, so that one group has taken her side another that of her parents, and indeed made it impossible to keep her [any] longer at home [Ref. 17, p 120–3].

It has been speculated that Adolf Hitler may have had encephalitis lethargica and that his obsessions and mannerisms may in part have been a manifestation of the residual effects of an attack of encephalitis lethargica during First World War.[18,19] Other prominent residual effects include an atypical form of Parkinson's disease, occurring weeks to decades after the acute stage of encephalitis lethargica, which is well illustrated in Oliver Sacks' book and subsequent movie, *Awakenings*.[20]

Herpes Simplex Encephalitis

Herpes encephalitis is caused by the herpes simplex virus, the most common manifestation of which is the cold sore. The virus is acquired early in life and infects most of the population. After the initial infection, the virus is present in the trigeminal ganglion in a latent state from which it reactivates periodically, often in response to a trigger (such as a febrile illness, exposure to ultraviolet light, and other stress). The reactivation can be manifested by a "fever blister" on the margin of the lip. Rarely and for reasons not completely clear, the reactivation occurs in the brain and appears to be responsible for many cases of herpes encephalitis, although some are due to *de novo* infection with herpes simplex virus.[21] When herpes simplex infects the brain, the resulting encephalitis preferentially affects the mesial temporal and inferior orbital part of the frontal lobes, including the limbic cortex. The clinical illness therefore often begins with behavioral problems and hallucinations, and the presence of the disease is suspected when the patient exhibits a fever, seizures, and focal weakness. Several detailed case descriptions from Drachman and Adams[22] illustrate this point and summarize the behav-

ioral presentations of their patients with herpes encephalitis:

> In 5 of the cases, the most striking initial symptoms were of a "psychological" nature. At first, the patients were only mildly ill, and only the aberrations of behavior called attention to the serious nature of the illness. Patient 1 dressed by lamplight to go to an imagined funeral. Patient 2 packed her suitcase almost a week in advance for a short journey. Patient 3 became confused and disoriented. Patient 4 failed to recognize his wife. Patient 5 slept until 4 pm one day, then suddenly rushed out of his house without explanation [Ref. 22, p 72].

Another case described by Johnson[23] further illustrates this point: "A dentist en route to work one morning entered his garage, came out with an ax, and chopped down his neighbor's picket fence [Ref 23, p 144]."

The damage to the temporal lobe structures that mediate memory formation and retrieval often leaves the patient with severe memory deficits, despite normal or above average intelligence. This is illustrated in the narrative below:

> [Several months after her acute illness, a teenaged girl's] greatest residual intellectual deficit was a severely impaired ability to form new memories. She was now alert, but was unable to learn even the simplest facts. Although she was incessantly drilled on the name of her doctor, she was never able to recall it from memory. She could not remember that she was at the Massachusetts General Hospital. On one occasion, just as she was swallowing the last spoonful of an ice-cream dessert, she was asked what she had eaten; she could not even recollect having eaten anything [Ref. 22, p 65].

The behavioral consequences of the damage to the frontal and temporal lobes in this particular patient is revealed in a further description of her behavior several months after her initial illness:

> . . .[A]t first she was unmanageable at home, tearing wallpaper off the walls, breaking dishes, and banging on the piano until her brothers refused to stay in the house with her. She bit her father several times, threatened to jump from a window, and spat continuously. The family was forced to put a "No Visitors" sign on the door; finally the patient was committed to a mental hospital for a 10-day period [Ref. 22, p 65].

The damage that occurs to the frontal and temporal lobes in herpes encephalitis can lead to violent and sexually inappropriate behavior.[24,25] In one case, an adolescent boy became so violent after herpes encephalitis that several residential facilities refused to keep him.[24]

Epstein-Barr Virus Encephalitis

Epstein-Barr virus, which causes infectious mononucleosis, can occasionally result in encephalitis. Most cases of EBV encephalitis are characterized by a febrile confusional state. Some cases exhibit unusual behavior. Cases of Alice-in-Wonderland syndrome have been recorded. In one case, a nine-year-old boy, after nine days of fever and sore throat, noticed that objects in his field of vision were changing in size, shape, and position, frightening him. His parents noted restlessness and a slight change in his behavior. He was found to have an acute EBV infection. The perceptual abnormalities resolved spontaneously, along with his febrile illness, over three weeks.[26] Another patient, a 35-year-old man, began to have fatigue, difficulty in concentrating, moodiness, and complained that people's faces appeared distorted. He was hyperalert, easily distractible, and had an abnormal mood. His electroencephalogram showed abnormalities in his right parietal lobe, and magnetic resonance imaging (MRI) showed an abnormal area in the right temporal region. These would explain his perceptual and behavioral abnormalities. Investigation of serum and spinal fluid showed evidence of recent infection with EBV, and a brain biopsy showed a demyelinating process, which can occur after a viral illness. All of these abnormalities resolved spontaneously over the next several months.[27] Two other patients exhibited prominent depressive symptoms, which were accompanied by minor neurologic abnormalities, mild cognitive changes and an abnormal electroencephalogram. Acute EBV infection was documented by serology. Both patients recovered, one with complete resolution of the symptoms and the other by adjustment to her mild intellectual deficits (her IQ was in the normal range, although her premorbid IQ was probably higher).[28]

Arbovirus Encephalitides

The term arbovirus refers to any virus transmitted by arthropods. In the United States this includes most commonly LaCrosse encephalitis, St. Louis encephalitis, western equine encephalitis, eastern equine encephalitis, and the emerging infection, West Nile virus encephalitis. The first two disease types are the most common in the United States, affecting tens to hundreds of people annually, depending on whether there is an epidemic present. The next two affect only a handful of people each year. At present, West Nile virus has become widely established in North America, with over 3,000 cases recorded in the United States during the summer of 2002.[29] Patients may have cognitive and emotional

difficulties that remain after the acute disease has resolved.

In a review of LaCrosse encephalitis, Rust *et al.* note: "Behavioral disturbances (emotional lability, hyperactivity, withdrawal, aggressiveness, excessive irritability) are common in the early convalescent phase of LaCrosse encephalitis" (Ref. 30, p 7). In most cases, however, these behavioral abnormalities eventually resolve completely.[30]

St. Louis encephalitis often leaves residual cognitive and emotional problems. It has been estimated that 20 to 50 percent of patients have nervousness, restlessness, irritability, fatigability, emotional lability, benign anxiety state, and personality change during convalescence, although most symptoms resolve over a few years.[31]

In a study of survivors of an epidemic of western equine encephalitis, 6 of 22 patients had severe deficits, especially in abstract thinking and planning, which is reminiscent of the frontal lobe syndrome mentioned earlier.[32] Personality changes after western equine encephalitis were also noted to be "prominent" by Herzon *et al.*[33] In fact, the personality changes may not be obvious during routine testing, and family reports may be crucial in uncovering these sequelae. According to Mulder *et al.*[32]:

> Certain sequelae were not obvious in specific testing situations but became apparent in the total life situation. The patient was often not aware of or concerned about these symptoms, but the immediate family was distressed to note deterioration in loved ones who had been fairly average in their adjustments prior to the illness [Ref. 32, p 322].

An example of such a case of western equine encephalitis follows:

> A 31-year-old male cook became ill. . .[and]. . .was admitted to hospital complaining of headache, drowsiness, muscle pain and malaise. . . . Shortly after admission, the patient became comatose and remained in coma for two weeks. . . . [His] temperature returned to normal. At this time his condition seemed greatly improved and he appeared to be making a good social adjustment. He was dismissed from the hospital to the care of his wife. . . . [F]our months after his acute illness. . .the patient himself had no complaints, except for the loss of tonal quality in his voice. His wife stated that he could not return to work because of hand tremors. She complained that he no longer cared about his appearance, that he drove through red lights, threw bills in the wastebasket remarking they were "only bills," and frequently threatened to harm his family. He spilled food on his clothing and on the floor, and to his family's dismay, he then picked it up and ate it. He did not wait for food to be served, but would snatch it off the platters with his fingers as his wife neared the table. His sexual activity became uninhibited, and he sought intercourse with neighbor children and prostitutes with no concern for possible consequences. He was committed to a state hospital four months after his acute illness [Ref. 32, pp 322–3].

Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a rare complication of measles (occurring in about 1 in 1 million cases of measles in childhood) in which the measles virus infects the brain during the initial disease and then remains quiescent for several years. The clinical illness begins with behavioral abnormalities, with unusual moodiness and deterioration of schoolwork. This progresses to memory difficulties, spasticity, myoclonic jerks, and dementia, eventually leading to coma and death.[34] The initial illness could lead to a suspicion of illicit drug use, but the neurological character of the illness becomes apparent within a few weeks to months. The disease has essentially disappeared from industrialized nations since the introduction of measles vaccination but is found in countries with poorly developed national vaccination programs.

HIV Disease

HIV infection is well known to result in a collapse of the immune system, but the virus also infects the central nervous system. The virus infects $CD4^+$ lymphocytes and macrophages, principal cells of immunity. It is not yet known how the virus gets into the brain, but brain macrophages and microglial cells are the main cells infected. There are virtually no neurons infected, and astrocytes appear to be infected but do not produce virus. Direct viral lysis of neural cells by HIV does not occur. Hence, the mechanism of injury by HIV in the central nervous system is indirect. One hypothesis, largely accepted, is that immune cells such as macrophages and microglial cells elaborate soluble factors that, in conjunction with viral products, induce a cascade of effects in other cells, such as macrophages, astrocytes, endothelial cells and oligodendrocytes, that then affect the function of neurons.[35]

Early in the course of HIV infection, there are few neurological problems, but later on, as the disease progresses, HIV motor-cognitive disorder or HIV dementia may develop, in which brain function is disturbed. In some patients, these disturbances remain mild and are labeled HIV-associated minor motor-cognitive disorder. The relationship between the minor motor-cognitive disorder and HIV dementia is not clear.

HIV dementia has three aspects: cognitive, behavioral, and motor. Cognitive dysfunction in HIV dementia consists of inability to sustain attention, forgetfulness, and disorganization of thought. More severely affected patients are unable to recall the salient points of newspaper stories, the plot of a movie they have seen, or how to drive home. They keep lists to remember what they have to do each day. Despite this, they are often unable to organize their day-to-day activities, and may get lost or confused about such simple matters as getting the groceries and balancing their checkbooks. Behavioral dysfunction consists of withdrawal from social interactions, irritability and irascible behavior, and a loss of interest in hobbies or other pleasurable activities. The irritability can become quite prominent.[35] Concurrent with the behavioral and cognitive problems, patients have difficulty with fine motor control, with clumsiness of the fingers in such activities as typewriting, and difficulty with gait. Many HIV-infected patients may also have serious mental illness and substance abuse, so-called doubly and triply diagnosed. The imposition of cognitive disability complicates and aggravates social integration for such HIV-infected individuals.

Conclusion

Personality and behavioral change can be prominent in infections of the brain. This occurs both in the acute illness and as a residuum of structural damage to the brain. Violence, theft, and antisocial behavior can be seen both in the acute illness and as sequels to the disease, resulting in incarceration. Some previously law-abiding patients have been arrested because of criminal behavior. Other patients have poor memory and an inability to organize behavior, leading to a dependence on others for their daily existence. Such patients have great difficulty in securing and sustaining a job, leading to disability, often when they are not obviously abnormal. Society's response to such compromised individuals should be therapeutic, not punitive. Attempts at rehabilitation, rather than incarceration, appear to be the most just and humane response.

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