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Neuropathological Findings in the Brain of Karen Ann Quinlan

The Role of the Thalamus in the Persistent Vegetative State

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ABSTRACT

Background Karen Ann Quinlan had a cardiopulmonary arrest in 1975 and died 10 years later, having never regained consciousness. Her story prompted a national debate about the appropriateness of life-sustaining treatment in patients who are in a persistent vegetative state and led to the development of medicolegal guidelines for the care of such patients. This report describes the neuropathologic features of Quinlan's brain.

Methods The entire brain and spinal cord were systematically sampled for histologic examination. The brain stem and central cerebrum were embedded en bloc and serially sectioned. Three dimensional computer reconstructions helped visualize the topographic features of the lesions.

Results Contrary to expectation, the most severe damage was not in the cerebral cortex but in the thalamus, and the brain stem was relatively intact. The neuropathological findings included extensive bilateral thalamic scarring, bilateral cortical scars primarily in the occipital pole and parasagittal parieto-occipital region, and bilateral damage to cerebellar and focal-basal-ganglia regions. The brain stem and basal forebrain and the hypothalamic components of the ascending arousal systems and brain-stem regions critical to cardiac and respiratory control were undamaged. The lesions were consistent with hypoxia-ischemia after the cardiopulmonary arrest.

Conclusions Although the neuropathological findings in the case of Karen Ann Quinlan were complex, the disproportionately severe damage in the thalamus as compared with the cerebral cortex supports the hypothesis that the thalamus is critical for cognition and awareness and may be less essential for arousal.

ARTICLE

In 1975 the case of Karen Ann Quinlan dramatized the moral and legal debate over life-sustaining treatment after the irreversible loss of all meaningful cognitive functions (1,2,3). After a cardiopulmonary arrest and coma, Quinlan was in a persistent vegetative state. Her parents sought permission from the court to let her die naturally by the discontinuation of "extraordinary" treatment -- in particular, mechanical ventilation -- which they thought was sustaining her "hopeless" condition. The Quinlans eventually won their case, and the ventilator was removed in 1976. Quinlan nevertheless survived another nine years in a persistent vegetative state. Her case led to the development of medicolegal guidelines for the care of such patients (2,3).

In the persistent vegetative state, there is wakefulness (arousal) but neither cognition nor awareness (3,4,5,6). Patients in this state have survived up to 37 years (6) with intact sleep-wake cycles and cardiopulmonary regulation but no manifestation of awareness, thought, or emotion (3,4,5). A full description of the persistent vegetative state appears elsewhere in this issue (6). This report

describes the neuropathological findings in Karen Ann Quinlan, thereby completing the clinical data in this landmark case.

Case Report

The clinical history and findings are based on examination of the patient by one of us, interviews with the attending physicians, and a review of all relevant documents, including medical and nursing records. At 21 years of age, Karen Ann Quinlan had a cardiopulmonary arrest after accidentally ingesting a combination of prescription sedatives and alcohol. When she was found, she was unresponsive, apneic, pulseless, and cyanotic with dilated pupils. She received cardiopulmonary resuscitation. In the emergency room, a pulse was present, but she was otherwise unchanged and was placed on a ventilator. Within the first hour after cardiopulmonary arrest, spontaneous respirations and normal vital signs had returned, but the patient remained unresponsive to noxious stimuli and was areflexic. During the first 12 hours, there was sequential improvement, with the development of pinpoint pupils and sluggish reaction to light, upper-extremity flexion, toe inversion, responsivity to pain, gag and cough reflexes, spontaneous movement of all extremities, and finally, opening of the eyes in response to auditory stimuli. Aspiration pneumonia led to a tracheostomy on the second day. Hypoxia occurred transiently, with a low arterial partial pressure of oxygen of 45 mm Hg. During the first week after the arrest, stimulus-induced postural patterns were seen, including flexion and clenching of the hands, plantar flexion and inversion of the feet, turning of the head to the right, **yawning**, and grunting. With intense stimulation, there was flexion of the upper and lower extremities with marked spastic rigidity, opisthotonos, and upward rolling of the eyes. There was no response to threatening gestures. Oculocephalic and oculovestibular reflexes had returned to normal. All extremities withdrew in response to a pinprick.

During the first six months after the arrest, Quinlan had unequivocal sleep-wake cycles but never showed signs of awareness of her environment or cognitive function. During sleep she rarely triggered the ventilator. Severe contractures developed, and orofacial movements (e.g., grimacing) dominated the arousal responses in association with marked diaphoresis, tachycardia, and tachypnea. Quinlan's movements were never goal-directed but always stereotypical and reproducible with a given stimulus. Although she had the full range of eye movement, her eyes moved randomly with occasional disconjugate components, and she never responded to stimuli with meaningful extraocular movements. Quinlan had sufficient primary motor competence to respond in a meaningful fashion had any cognitive function been intact, which buttressed the clinical diagnosis of a persistent vegetative state, not a locked-in state (i.e., conscious but with severe paralysis, making vocal communication impossible). A brain scan and bilateral carotid and vertebral angiograms were unremarkable. Electroencephalograms showed cortical activity (predominantly low-voltage fast activity [beta]) when the patient was awake. When she appeared to be asleep, there was intermittent low-voltage activity of 3 to 7 Hz , infrequent activity in the alpha range, and occasional slower activity in the delta range. During the first six months after the arrest, the patient became severely cachectic, and her weight stabilized at 32 to 34 kg (down from 52 kg) with hypercaloric feeding. Multiple lung, bladder, and decubitus-ulcer infections were treated.

During the second six months after the arrest, Quinlan began to trigger the ventilator more frequently while asleep, and she was weaned from it over a period of a month, one year after the arrest. Seizures (episodic twitching of the extremities, mouth, and eyes for about 30 seconds) developed and were successfully treated with phenytoin. A computed tomographic scan five years after the arrest revealed cerebral and cerebellar atrophy with generalized dilatation of ventricular and

cisternal systems. Fourteen months after the arrest, Quinlan was transferred to a nursing home where she remained in a persistent vegetative state until her death nine years later from overwhelming infection.

General Autopsy Findings

An autopsy was performed 13 hours after death. The immediate cause of death was a combination of bacterial bronchopneumonia, vegetative endocarditis, and meningitis. The findings included severe cachexia (body weight, 27 kg); hyperextension of the neck with deviation of the face to the right; severe flexion contractures and skeletal-muscle atrophy; chronic decubitus ulcers; septic emboli in the heart, kidney, spleen, and small intestine; a subacute renal infarct; and adrenal lipid depletion.

Neuropathological Findings

The brain and spinal cord were fixed in 20 percent formalin for three years. The central cerebrum from the frontal horn to the atria of the lateral ventricles was embedded en bloc in paraffin (Paraplast) and cut into serial sections that were 20 microm thick. This cerebral block contained the entire thalamus, hypothalamus, basal ganglia, hippocampus, amygdala, basal forebrain, temporal lobe, posterior frontal cortex, and parietal cortex to the level of the atria. Six other cerebral blocks, anterior and posterior to this large block and approximately 5 mm thick, were processed similarly. Sections every 2 mm were stained alternately with a combination of hematoxylin and eosin and Luxol fast blue and with cresyl violet. The brain stem was embedded in toto and sectioned serially; alternating sections every 260 microm were stained with hematoxylin and eosin and Luxol fast blue or with cresyl violet, and selected sections were immunostained for glial fibrillary acidic protein. Representative sections of the cerebellum and spinal cord were also examined. To help correlate the clinical and anatomical findings, three-dimensional computer reconstructions were generated from serial sections of the central cerebrum and the entire brain stem (7). For the reconstruction of the cerebrum, every 100th section (a total of 22 sections) was analyzed, and for the reconstruction of the brain stem, every 60th section (a total of 40 sections) was analyzed. A three-dimensional atlas of the distribution of lesions was made by computerized digitization of the boundaries of individual nuclei, fiber tracts, and lesions (7). Reference atlases of the human thalamus and brain stem were used (8,9).

The unfixed brain was underweight (835 g; normal weight, 1300 g) owing to atrophic tissue, primarily in the cerebral cortex, cerebellum, and thalamus. Bacterial meningitis with microabscesses scattered throughout the brain parenchyma, representing the terminal process, did not compromise the assessment of the underlying, long-standing brain damage. Cortical scarring was severe in the parasagittal region bilaterally from the precentral gyrus of the posterior frontal lobe to the parieto-occipital fissure in the distribution of the arterial border zones of the middle, anterior, and posterior cerebral arteries (Figure 1, 2, and 3). Neuronal loss with gliosis was severe in this parasagittal lesion, and there was loss of myelin and gliosis in the underlying white matter, associated corpus callosum, and superior portions of the posterior limb of the internal capsule (Figure 2 and Figure 3). The parietal cortical atrophy involved superior areas 5 and 7 but spared inferior areas 39 and 40. The occipital poles, including the primary visual cortex (area 17), were also severely atrophic bilaterally, with profound neuronal loss, gliosis, and myelin loss. Focal, microscopic scars (minimal-to-moderate neuronal loss and gliosis) were identified in the insula, cingulate gyrus, orbitofrontal cortex (the arterial border zone of the anterior and middle cerebral arteries), and parahippocampal gyrus bilaterally (Figure 3). Throughout the remaining cerebral cortex, there was

no obvious neuronal loss (Figure 4). In several prefrontal regions there were subtle focal increases in astroglial nuclei, particularly in the upper laminae, but neuronal loss was not apparent. The central white matter was characterized by a mild pallor of the myelin in the prefrontal and temporal lobes bilaterally, but there was no reactive gliosis or obvious breakdown of myelin. There was moderate hydrocephalus ex vacuo (Figure 2). Wallerian degeneration was present in the corticospinal tracts bilaterally.

The thalamus was bilaterally and symmetrically atrophic (Figure 2, 3, and 5). Damage was characterized by gliosis and neuronal loss ranging from minimal to complete within individual nuclei (Figure5). The extensive damage obliterated the cytoarchitectonic boundaries and resulted in overall contraction and anatomical distortion of the thalamus; nevertheless, efforts were made to assess the degree of involvement within a nucleus by correlating the lesion with the approximate boundaries of the nucleus in reference atlases8. The most severe damage was in a paramedian and lateral distribution, particularly in the central and posterior portions, and involved the anterior, ventral lateral, dorsomedial, and lateral posterior nuclei (Figure 5). The pulvinar was also severely affected but contained islands of residual neurons. The ventroposterior lateral and medial nuclei were moderately involved. Damage in the intralaminar nuclei ranged from mild (in the parafascicular nucleus) and moderate (in the centromedial nucleus) to severe (in all others). There was severe neuronal loss in the middle-to-posterior portions of the reticular nucleus. The medial and lateral geniculate nuclei were severely affected medially, and there was wallerian degeneration of the optic radiations. There was virtually no damage in the midline paraventricular nucleus, medioventral nucleus, lateral dorsal nucleus, and subthalamic nucleus bilaterally. The zonae incerta and pretectum were mildly gliotic.

In the caudate nucleus and putamen, there was bilateral and symmetric neuronal loss and gliosis in the posterior and superior regions, and there was mild gliosis in the globus pallidus. The nucleus basalis of Meynert, septal nuclei, amygdala, and nucleus accumbens were histologically intact. In the hypothalamus, the nuclei appeared to be intact, except for the mamillary bodies, in which there was severe neuronal loss and gliosis; the fornix, alveus, and fimbria were pale. There was neuronal loss and gliosis in area CA4 of the hippocampus. The entire cerebellum was severely sclerotic (Figure 1), with loss of Purkinje and granule cells, Bergmann gliosis, and demyelination. Neuronal loss was severe in the dentate nuclei.

Brain-stem regions subserving arousal, sleep, autonomic and ventilatory control, and upper-airway regulation were histologically intact. These regions included the reticular formation (e.g., the nucleus pontis oralis, nucleus pontis caudalis, and nucleus paragigantocellularis lateralis), locus coeruleus, interpeduncular nucleus, raphe nuclei, parabrachial complex, vagal nuclei, and hypoglossal nucleus. The one exception was the rostral nucleus cuneiformis (midbrain reticular formation), which was slightly gliotic. In the inferior olive (cerebellar relay), there was severe neuronal loss and gliosis bilaterally; these changes were considered secondary to retrograde transsynaptic degeneration from the widespread loss of Purkinje cells. There was severe neuronal loss, gliosis, and axonal spheroids in the nuclei gracilis and cuneatus medialis, with bilateral degeneration of the posterior columns, which was most pronounced in the cervical fasciculus gracilis. Myelin staining was slightly pale in peripheral nerves.

Discussion

The pathologic features of Karen Ann Quinlan's brain included bilateral and symmetric damage in

the thalamus; bilateral scars restricted primarily to the parasagittal parieto-occipital region and occipital pole in an otherwise relatively well-preserved cerebral cortex; bilateral damage to cerebellar and focal-basal-ganglia regions; and relative sparing of the brain stem, basal forebrain, and hypothalamus, with the exception of atrophic mamillary bodies. The lesions were consistent with hypoxic ischemic injury and cerebral edema due to the cardiopulmonary arrest that had occurred 10 years before death. An analysis of these lesions suggests at least three mechanisms of damage: a hypoxic insult to vulnerable neuronal populations (e.g., the cerebellar cortex), ischemic damage to arterial border zones (e.g., the parasagittal parieto-occipital region), and ischemic damage due to vascular compression from possible brain herniations that were partial or were reversed immediately after the cardiopulmonary arrest (e.g., the calcarine cortex in the posterior cerebral-artery distribution) (10). The hypoxic ischemic damage to the thalamus may reflect a combination of compressive and intrinsic susceptibility factors, with the most severe damage in the paramedian and posterolateral regions supplied primarily by the thalamogeniculate branches of the posterior cerebral artery. The degeneration of the posterior column probably resulted from nutritional deficiencies and compression of the peripheral nerves, which are recognized complications of the persistent vegetative state (11).

The persistent vegetative state raises fundamental questions about the neuroanatomical basis of human consciousness and the nature of brain damage that leads to a dissociation of cognition and awareness from arousal4. Previous clinical and anatomical studies of the persistent vegetative state have reported extensive bilateral damage to the cerebral cortex, sometimes approaching total decortication, with variable involvement of subcortical regions (including the thalamus) and sparing of the brain-stem regions that control ventilation, autonomic activity, and pupillary function (12,13,14,15,16,17). Separation of the cerebral cortex from its subcortical connections by widespread, bilateral demyelination has likewise been observed (18,19). Such reports reinforce the accepted role of the cerebral cortex in cognition and awareness and of the brain stem in the vegetative state. In Quinlan's case, however, the most extensive and bilateral damage was not in the cerebral cortex or white matter. In other patients in the persistent vegetative state, cerebral cortical damage has varied widely, and as in Quinlan, has sometimes seemed insufficient to cause the global defects (4). One explanation emphasizes the extensive connections between cortical regions and suggests that focal cortical damage may alter function in undamaged regions (4). Another explanation attributes the global defects to the cumulative effect of a combination of cortical or subcortical lesions (20). The presence of bilateral lesions in the thalamus observed in Quinlan as well as in other patients (16,21,22) however, suggests that widespread damage to this structure may produce or contribute substantially to a clinical state similar to that resulting from widespread and bilateral damage in the cerebral cortex or white matter alone.

The hypothesis that the thalamus plays a key part in the persistent vegetative state is supported by the highly interdependent relation between the thalamus and the cerebral cortex and by increasing recognition of the role of the thalamus in cognitive processing. Several studies suggest that cognitive functions are mediated by parallel distributed networks in the association cortex (23,24,25,26,27). The vertical column, considered the basic unit of the cerebral cortex, forms information-processing modules with adjacent columns that are connected with other specific cortical and subcortical regions, including thalamic nuclei (23,24,25,26,27). Components of a particular cognitive function are distributed among the connected regions in a particular network, with each region involved in a different aspect of the function; consequently, lesions in one region of a network may impair that region's component of cognitive ability or all the components mediated by the network as a whole (23,24,25,26,27,28). The idea that thalamic nuclei are critical components of distributed networks is

supported by clinical observations that a lesion in a thalamic nucleus that is preferentially connected with a particular region of the cortical association (e.g., the dorsomedial nucleus with the prefrontal cortex) results in functional impairment similar to that associated with damage in the cortical region itself (26,28,29,30,31,32). In Quinlan's case, some of the most severe damage was in thalamic nuclei closely connected with regions of the cortical association that are involved in multiple and diverse cognitive functions, including selective attention, (23,26,28,29,30,31,32) suggesting that this damage was the chief cause of her global impairment. This idea is further supported by reports of dementia that is indistinguishable from that produced by diffuse cerebral cortical disease in patients with bilateral tumors, infarcts, or degeneration restricted to the thalamus (28,33,34).

Quinlan had intact arousal in spite of extensive bilateral damage in the thalamus. Historically, arousal has been thought to be dependent on the activation of the cerebral cortex by a relay of inputs from the brain-stem reticular formation through diffuse and widespread projections from the intralaminar and midline nuclei of the thalamus (known as the reticular activating system) (26,28,35,36,37). In addition, the thalamic reticular nucleus has been described as the pacemaker that globally modulates thalamic activity during various levels of arousal from brain-stem inputs (36,37). Recently, however, the essential role of the thalamus in arousal has been challenged, in part by the recognition that the cerebral cortex can be directly activated by cholinergic, serotonergic, noradrenergic, and histaminergic arousal systems that originate in the brain stem, basal forebrain, or hypothalamus and do not project through the thalamus (35,36,37,38,39). In Quinlan's case, the relative sparing of these components of the extrathalamic ascending arousal systems, in association with bilateral thalamic damage and only a focally damaged cerebral cortex, supports the hypothesis from studies of animals that thalamic and extrathalamic pathways mediate arousal in parallel and that the thalamus may not be essential for arousal when the extrathalamic pathways are intact. Residual neurons were present in intralaminar and reticular regions in Quinlan's case, and certain midline nuclei were spared. Thus, arousal may have resulted from a combination of extrathalamic and residual thalamic activation. Nevertheless, the findings in her case reinforce the idea that arousal is mediated by pathways that are separate from those involved in cognition and awareness and suggest that stimulation of the cerebral cortex by thalamic and extrathalamic ascending systems may be sufficient for arousal but not for cognition and awareness (which nevertheless depend on arousal) (4). The persistent vegetative state in Ms. Quinlan probably did not result from thalamic damage alone. It is likely, for example, that lesions in the parieto-occipital border zones contributed to the attention defect, because the involved parietal area is part of the distributed attention network and isolated bilateral parietal lesions can result in inattention to visual stimuli (26,28). The multiple focal lesions in Quinlan's brain may support the hypothesis that the persistent vegetative state results from a complex interplay of discrete cortical and subcortical damage and represents the sum of primary and secondary pathogenic factors, which varies among patients, particularly since lesions in the persistent vegetative state are virtually never restricted to a single locus (12,13,14,15, 16,17, 18, 19,20,21,22). However, focal extrathalamic lesions such as those observed in Quinlan (parasagittal atrophy, occipital atrophy, and cerebellar sclerosis) are not themselves known to cause global deficits in cognition, awareness, and affect (26,28,40,41). Extensive thalamic damage with little or only focal damage in the cerebral cortex has been noted in other patients in the persistent vegetative state (16,21,22). Such thalamic damage, however, has been related primarily to the role of the thalamus in the reticular activating system(16) and, more recently, to its role in cognition, (22) as we have emphasized in Quinlan's case.

Similarly, previous reports have considered thalamic neuronal loss in the persistent vegetative state to be secondary to transsynaptic degeneration from cortical lesions or to be too small to result in global deficits (13). The severity, uniformity, bilaterality, and vascular topographic features of the

thalamic damage in Quinlan's case suggest that it was primary damage after the cardiopulmonary arrest. The gliosis observed in focal cerebral cortical regions, on the other hand, may reflect subtle neuronal loss secondary to transsynaptic degeneration from thalamic damage and long-standing cortical deactivation and decreased use of oxygen and glucose in the persistent vegetative state (42,43).

In conclusion, although the neuropathological findings in Quinlan's case were multifocal and complex, the disproportionately severe and bilateral damage in the thalamus as compared with the damage in the cerebral cortex supports the hypothesis that the thalamus is critical for cognition and awareness and may be less essential for arousal. Taken with emerging information about the part that the thalamus plays in cognition and reports of thalamic dementia, these findings point to the role of the thalamus in the pathogenesis of the persistent vegetative state.

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Source Information

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