Chronic "brain death": meta-analysis and conceptual consequences
Antonio López-Navidad
Neurology 1999;53;1369

This information is current as of July 24, 2011

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http://www.neurology.org/content/53/6/1369.full.html

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Chronic “brain death”: meta-analysis and conceptual consequences

To the Editor: The concepts that Dr. Shewmon1 brands on death, chronicity, somatic integrative unity, and survival, and the articles on which he bases his arguments, suffer from such manipulation that the results become antithetical. His application of statistical methods exemplifies how statistics can be transformed into nonsense.

Death cannot be chronic; it always occurs from one second to the next. At a given moment you are alive and at the next moment you are dead—you no longer exist—and starting from that moment death is forever. Nothing can modify the situation. The concept of brain death (BD) as death of the individual is based on this concept and not on the irreversible asystole that will occur, always and without exception, in less than an hour in all BD heart-beating cadavers when artificial means of support are removed. That a family can reach the point of wishing to take away the collection of organs covered by a protection of skin and bones, and in whose cranial cavity the maceration of the nervous tissue allows the detritus of a cortical neuron to remain floating among the remains of others from the putamen, to carry out maintenance at home with “minimal” artificial means (e.g., mechanical ventilation; strict, assisted control of the temperature, diuresis, nutrients, and ions; pulmonary infections) is a monstrosity that would have to be considered as a serious form of psychopathology of bereavement, a model probably induced in the doctor who had been responsible for what is now a cadaver.

The somatic integrative unity of the BD heart-beating cadaver proclaimed by Shewmon does not differ substantially from that obtained by Alexis Carrel over 60 years ago, when he extracted the thoracic and abdominal contents of a cat en bloc and maintained them with the heartbeat preserved, suspended in a vat with Ringer’s solution for hours. Nor does it differ, either conceptually or substantially, from what we obtain with cadavers in exceptional cases. The successful pregnancy cases are not a representative sample because publication bias undoubtedly is present; only occasionally are failures of attempted support published.2,3 These cases are anecdotes yearning for a denominator.

Validity of the BD diagnosis. BD declarations are not inherent, unreliable but often prematurely performed incorrectly. A recent prospective study of BD determination in pediatric intensive care units found marked variation in the diagnosis of BD. In a series of 93 children who were considered BD, more than half were diagnosed by criteria departing from published guidelines for the determination of BD. Thirty-eight patients gave a consent for organ preservation, but procurement in another 20 patients fortuitously was halted after a careful neurologic examination. Accordingly, we respectfully remain skeptical about whether all the reported cases represent valid BD determinations. First, in only 2 of the 56 cases were apnea tests performed with documentation of absent respiratory effort at a PCO$_2$ of 60 mm Hg. Many cases included only brief (minutes) disconnection of the ventilator, an inadequate apnea test. Second, many cases did not have documentation of the details of neurologic examination (“brainstem reflexes absent,” “brain death was declared”), a group bucking to tracheal suctioning was not mentioned, and examination of the patients by at least one neurologist was inconsistent. Surprisingly, some reports documented motor responses (“nonpurposeful withdrawal to pain,” “decerebrate responses”) incompatible with BD. Cases extrapolated from circumstantial evidence in newspapers cannot be taken seriously. Retrospectively analyzing the existing literature remains an inexact science, and from the macabre case of child “T.K.” seen in the press, with no full BD assessment (not even at the presence of septations on MRI)1 Septations suggest tissue organization and tissue organization requires intracranial blood flow. MR angiography may not be as sensitive or specific as conventional cerebral angiography.

Complexity of care and survival. Details are absent on the day-to-day care in most cases and there may be publication bias toward the best managed cases. In our medical era, technology may temporarily replace critical brain functions. Novitzky’s catecholamine storm theory of the production of cardiac damage is not shared by recent investigators, who claim that the hemodynamic changes in BD persons are a consequence of severe sympathetic withdrawal and not myocardial damage.5 These patients are all immobile, and their vascular tone can be maintained owing to spinal reflexes. We suspect a simple tilt test would lead to immediate cardiovascular collapse. Many viscera contain their own pacemakers. The heart continues to generate a forceful pulse, and even the gastrointestinal organs have endogenous properties in their systems and all the machinery required to maintain electrical currents. The levels of most pituitary hormones do not decrease significantly after the diagnosis of BD is made because of the extracranial circulation to the pituitary. In addition, luteinizing hormone and growth hormone were detected in plasma in patients with autopsy-proven extensive brain necrosis, suggesting hormone release from the pancreas, intestine, or adrenal gland, thus preserving some hypothalamic-pituitary axis.6 One might also speculate the effect of placenta-produced trophic hormones in pregnancy cases.

Antonio López-Navad, MD, PhD, Barcelona, Spain

To the Editor: The times have been
That, when the brains were out, the man would die,
And there an end. But now they rise again,
With twenty mortal murders on their crowns,
And push us from our stools. This is more strange
Than such a murder is.
Shakespeare, Macbeth (Act 3, Scene 4)

Alan Shewmon’s provocative article on “chronic brain death” describes a series of patients who presumably fulfilled accepted tests for BD but then were physiologically maintained for varying intervals until the point of asystole.1 He argues that the existence of such cases damages the coherence of the concept of BD because they show that bodily demise does not necessarily follow rapidly after the event of death. We wish to rebut the relevance of these cases to the concept of BD.

Methodology and the denominator. It is important to further analyze the cases reported by Shewmon in light of the supplementa-

These patients have already died. Chronicity indicates only that their bodily decomposition has been delayed until their circulation has ceased and is a direct consequence of their technological support within the modern intensive care unit.

The presence of these cases does not significantly diminish the validity of the concept of BD as human death. The whole brain remains the critical system responsible for the unity of the human organism. When it is destroyed or permanently ceases its clinical functions, the human being is dead irrespective of the artificial support of respiration and circulation.\(^{11,12}\) Neither we nor Macbeth have to fear phantasms; we all are dead when our brains are dead.

Eelco F.M. Wijdicks, MD, Rochester, MN; James L. Bernat, MD, Lebanon, NH

To the Editor: Dr. Shewmon's\(^1\) accurate article suggests a disturbing scenario of functionally beheaded bodies maintained in an artificial "life." What purpose does this serve? After such a thorough study he cannot avoid some other considerations.

He demonstrates that BD does not necessarily lead to imminent asystole and that our technology may obtain a "chronic brain death" (I prefer to place the whole expression in quotation marks on account of its semantic absurdity.) But he demonstrates also how perversely such technology may be used to keep a body functioning for over 14 years (the boy he named "I.F.K.") for no purpose. He does not suggest that such bodies may serve as organ donors, which would be a provocative but still a reasonable purpose; obviously he cannot give any hope for resurrection; and the conceptual consequences are unclear.

Why should these bodies be maintained in function? Just to say that we are another step ahead to becoming immortal, the next step being transplantation of new heads on the bodies? This is another example of what science and technology could do, but should not do.

Claudio Crisci, MD, Telese Terme, Italy

To the Editor: If anybody would have nurtured any doubt on the irreversibility of BD, Shewmon, in a recent article,\(^1\) has certainly silenced the most stubborn critic. Some may find that ventilating a brain-dead body for more than 5,000 days is more perverse than illuminating, but the absence of change among 56 cases even after prolonged observation periods only bolstered the aforementioned conclusions. Shakespeare was right when he stated (Macbeth, Act 3, Scene 4) “when the brains were out, the man would die.”\(^{14}\) Shewmon, however, alludes to the argument that BD signifies death because it is invariably followed by cardiac arrest within a couple of days. This is blatantly wrong, and the author is unequivocally right if he states that there must be other, better reasons for such an equation.

One is that everything that is considered specifically human, be it from a phylogenetic or ontogenetic perspective, is tightly linked to a functioning brain. Containing about 100 billions of neurons it is by far the most complex organ in this universe,\(^15\) although it may come up for only 2% of the whole body weight or consume only 20% of its energy. It is the only organ that cannot be transplanted—not even theoretically.\(^{16}\) Everybody would instantly and intuitively claim that a brain would receive a new body and not vice versa. Connectionism notwithstanding, it is not one organ among many equally important ones. Alas, I would not consider a brain in a nutritional solution a man or woman, but I would certainly agree that BD is human death in nuce. It is correct to say that with the permanent, irreversible loss of content the specific human features have been extinguished forever, whether the heart is still beating or not.

Because there is firm evidence that all consciousness and the capability to function as a whole\(^17\) are contingent on the structural and functional integrity of widespread areas of the brain, we should not dare to reduce whole BD to less than that. To talk about "partial brain death" is indeed a step on a slippery slope that may eventually dissolve stringent criteria. The acceptance of BD as a biological phenomenon that constitutes human death also from a legal perspective is conquering the globe, one notable exception being China. Of course, what death signifies is and has always been a consensus among the proponents and members of society. It may be subject to change, as history shows. But there is a growing conviction that BD should rightly be considered human death. Because it is a concept that on anthropologic grounds claims validity per se, it cannot be invalidated nor supported
by a time lag between BD and cardiac arrest. It does not imply that a person is going to die, and Shewmon is negating this when he says that a brain-dead body may “survive.” Who survives? It is quite another question to what degree of certainty BD can possibly be diagnosed. Here the author, who has cast doubt on it,12,20 must be contradicted. The only published cases in whom nonsignificant neurologic change occurred was in infants 3 months of age or less,21,22 giving rise to demanding additional perfusion imaging in this age group.

Because foreseeing the future with absolute certainty is impossible a priori, a grain of uncertainty must remain. It is astonishingly rare to hear doubts on the traditional concept of death (TD) by rigor mortis, livor mortis, and eventually putrefaction, although some errors occur every year. From talking to my colleagues and reviewing the scientific literature and mass media, I am more convinced than ever that the diagnosis of death by BD criteria is safer than the diagnosis of TD based on muscular, dermal, or olfactory criteria, which are nevertheless considered gold standard.

At a population of 265 million and a death rate of 0.9% per annum, approximately 2.4 million Americans die every year, about 0.8% (19,200) through BD. Let us assume that the ascertainment of each of the signa mortis is fraught with an error probability of 1 in 1,000 (N = 2), and there have been BD worldwide since 1959, then the odds are far below 1 in 1,000,000,000,000,000,000. This means that the false diagnosis is virtually excluded, provided that the criteria are not willfully neglected. So much for the cross-sectional validity.

As for the longitudinal validity, another consideration may elucidate the problem. If it is true that according to Bayesian statistics the error probability for any further false diagnosis after N correct diagnoses (N = 2), and there have been BD cases (by a clinical team oriented to the best interests of patient and family. The heterogeneity of outcomes also argues for heterogeneity of “fullness” of support (e.g., should management without vasopressin and epinephrine be considered “full” for research purposes)?

I emphasize that the number of cases found was ~175, not 56. For those reported as grouped statistics I tried to obtain individualized information, but in the end only 56 could be meta-analyzed. This in no way minimizes the significance of the remaining ~119 cases as to prolonged survival capacity.

I share Wijdicks’ and Bernat’s concern for diagnostic accuracy. Where we seem to differ is in the evidentiary standard that should apply to such a study. They seem unwilling to consider a case unless every detail be handed to them, including final pCO2 of the apnea test. Either we take what information we can get and try to learn from it what we can, or we concede to others to ignore a very interesting and conceptually important phenomenon. Only 11 of the ~175 cases came exclusively from newspaper reports. The remaining ~164 involved professional sources (a few had mixed sources). Nearly all diagnoses were confirmed by at least one neurologist or neurosurgeon. If a neurologist tells me (or tells a reporter) that a patient fulfilled standard diagnostic criteria, I have no a priori reason to doubt it. The patient was an organ donor or had support terminated, but to reject it if somatic survival lasted longer than a week, represents a question-begging double standard.

The dogma of invariably imminent asystole long predated standardization of apnea testing. If Wijdicks and Bernat would throw out all my cases in which the pCO2 level was not explicitly reported, they should equally not have considered all pCO2 levels usually cited as evidence for invariably imminent asystole. The article by Mejia and Pollack documenting a shocking lack of diagnostic standardization in practice cuts both ways. If Wijdicks and Bernat really believe that it invalidates our study, they should, to be consistent, more importantly direct their critical efforts toward a moratorium on transplantation until our profession gets up to diagnostic snuff.

Consider the remarkable case of the 14-year-old girl with survival >411 days, most of which was at home. Numerical apnea-testing data (pCO2 = 77) became available to me after my article went to press. Would Wijdicks and Bernat assert that the neurologists at University of Pittsburgh do not know how to diagnose BD or did not do so properly in this case? Did my previous lack of possession of their pCO2 data render their diagnosis inherently untrustworthy?

“Nonpurposive withdrawal to pain” in the context of BD is a spinal reflex compatible with the diagnosis. Of course “decerebrate responses” are incompatible with BD. I would like to know which reports Wijdicks and Bernat refer to as “documenting” such responses; I have read them all carefully and am unaware of any description of decerebrate responses after BD was diagnosed. Concerning “T.K.”s” MRI, the return of blood flow after a period of no flow is a well-documented phenomenon and is probably not uncommon in cases supported more than a few days.
I stand by what I stated in my article: “If patients were ‘brain dead’ enough to qualify as organ donors, they were surely ‘brain dead’ enough to qualify for this study.”

Dr. Lang’s bone of contention regarding diagnostic certitude is not against me but against misinterpretations of two earlier articles of mine. The statistical article did not maintain that brain cannot be diagnosed with certainty, but merely that certainty of functional irreversibility can derive only from knowledge of supracritical diffuse structural damage, not from the mere fact that functional criteria have been correct in N cases so far. The article about coma prognosis is irrelevant to BD diagnosis. Dr. Lang’s hypothetical example of error probability is miscalculated: the figures of 0.011 and 0.012 would represent the probability that all three or all eight diagnostic components would be wrong simultaneously. The probability of a correct diagnosis would be 0.998 and 0.999 ( = 0.957 and 0.922), and the probability of an erroneous diagnosis would be 1 minus that. The example does not seem particularly useful.

Ironically, the exceptional survivals may shed light on why the majority of BD bodies are so unstable. Most of the prolonged cases were also highly unstable initially. Only after some weeks could pressors be successfully discontinued, along with return of intestinal motility and prominent spinal reflexes, suggesting that the acute instability characterizing BD in general may be due not so much to mere absence of brain function as to diastasis or spinal shock. This theme is developed at length in a recent article.25 The transience of the instability suggests that in cases where multiple organs are not damaged by the initial etiology, if intensive care were maintained (not that it should be), those who make it through the difficult initial phase of spinal shock (especially children) would have the potential for much longer survival even without “heroic” support. Severe spinal shock should not be conflated with cessation of the organism as a whole.

Gradual hemodynamic stabilization over weeks is surely an integrative function at the level of the organism as a whole. The collected cases exhibited other integrative functions as well, such as homeostasis, wound healing, overcoming infections, autonomic stress reactions, proportional growth, gestation of a fetus, and even sexual maturation. The critical distinction between a sick, comatose body and a dead body has not been adequately characterized in the BD literature. I make a pass at it in a forthcoming article.26 But to equate physiologically, as Dr. López-Návidad does, such bodies with a bunch of excised viscera floating in a vat for a few hours, temporarily interacting but without holistic properties, is utterly ludicrous.

The second International Symposium on Brain Death in 1996 (the third is scheduled for February 2000 in Havana) evidenced a growing disillusionment with the biological organism-as-a-whole rationale and a leaning toward the personhood rationale. In fact, during the peer review of my article, the editor even opined that many readers of Neurology will probably consider the “organism” rationale outmoded, and that I was just preaching to the choir! Indeed, what could be more incoherent than to insist that a hemodynamically unstable body with diabetes insipidus and without brain function except for one minimally reactive pupil is a living “organism as a whole,” whereas a hemodynamically stable body with normal fluid homeostasis whose pupil does not react is a mere “collection of organs” or “a magnificent cell culture system”?

D.A. Shewmon, MD, Los Angeles, CA

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References

Posterior leukoencephalopathy without severe hypertension: Utility of diffusion-weighted MRI

To the Editor: Ay et al. demonstrate in their three cases that apparent diffusion coefficient (ADC) maps and diffusion-weighted imaging (DWI) can differentiate between posterior leukoencephalopathy syndrome (PLES) and early cerebral ischemia.1 They focused on the MRI changes without giving weight to the clinico-radiological dissociation, which is important to recognize these shadows. They describe three patients who did not show clinical signs that correspond to extensive shadows. Patients suspected of early ischemic infarcts usually have neurologic signs more pronounced than the radiologic counterparts. Also, the shadows described do not correspond to any specific arterial supply territory. Furthermore, we expect that ischemic infarcts of such magnitude will not be predominantly confined to the white matter without involving the gray matter as well. The authors indirectly imply the importance of hypertension in PLES by stressing the absence of severe hypertension in their cases. We think that seizures are more important in causation of PLES than hypertension. Conditions that cause PLES, such as eclampsia, hypertensive encephalopathy, immunosuppressive drugs, and renal disease, have seizures as their common denominator.2 Simi- lar data were reported in the absence of hypertension as reversible MRI abnormalities after seizures.2,3 Two of the three cases had seizures: one had generalized tonic-clonic convulsions and the other had partial complex seizures that are documented in experimental animals to cause such shadows.4 It is possible that the third patient had an unnoticed seizure during sleep. We believe that using the term PLES is misleading and inaccurate because the shadows may extend beyond the posterior region and beyond the white matter. In fact, the white matter is an innocent bystander; the vasogenic edema is present in the absence
of pathologic changes in the white matter itself. We believe that PLES is seizure-induced reversible shadow in a brain where autoregulation has been disrupted.

Tahir Obeid, MRCP, Jeddah; Adnan Awada, MD, Riyadh, Saudi Arabia

Reply from the Authors: Drs. Obeid and Awada claim that “seizures are associated with similar MRI changes” and propose that “PLES is indeed a seizure-induced reversible MRI shadow.” In fact, diffusion-weighted imaging (DWI) studies in animal models of status epilepticus (SE) as well as the study cited by Drs. Obeid and Awada indicate that ADC is reduced in SE in a time-dependent manner, leading to appearance of a bright signal on DWI. This is opposite to the finding of elevated ADC in our patients, indicating that MRI changes in PLES are unlike those reported in SE.

It is best to define radiologic findings by describing the signal characteristics on each image. In our patients with PLES, we describe an MRI signature comprised of signals elevated on ADC, normal or reduced on DWI, and elevated on T2-weighted images. This signature refers to increased water content in the posterior brain regions, mainly of vasogenic type. What makes this MRI signature noteworthy is that in PLES, extensive, sometimes life-threatening, vasogenic edema is the primary event and is not associated with brain infarction, hemorrhage, or mass-occupying lesion. It is possible that seizures or the other toxic-metabolic factors described may cause or aggravate vasogenic edema. However, it is notable that none of our patients was in SE during the course of their disease.

We agree with Drs. Obeid and Awada that the clinical findings in PLES are not sufficiently specific. In this respect, clinical differentiation of PLES from cerebral ischemia in the territory of the posterior circulation may be difficult in an emergency or when a patient first presents to a physician. At the initial stage of both disorders, CT and conventional MRI are either normal or demonstrate patchy, hyperdense intensities along the course of basilar and posterior cerebral arteries. Prominent changes on these images indicating nonterritorial pattern of involvement become evident only after a few days—a time point which, when reached, inevitably indicates that a “reversible” syndrome has not yet improved. DWI plays a pivotal role in the early but accurate differentiation of PLES from irreversible ischemia, rendering itself a clinically useful tool.

Hakan Ay, MD, Ferdinando S. Buonanno, MD, Pamela W. Schaefer, MD, Dean A. Le, MD, Bing Wang, MS, R. Gilberto Gonzalez, MD, PhD, Walter J. Koroshetz, MD, Boston, MA

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References

Phenotypic variation in leukoencephalopathy with vanishing white matter

To the Editor: We read with interest the recent article by van der Knaap et al. They reported cases of late onset leukoencephalopathy with vanishing white matter and assumed that “MRS and histopathologic features are compatible with a primary axonopathy rather than primary demyelination.” We recently reported the neuropathologic and biochemical features of two young patients with early onset cases of this type of leukoencephalopathy. Our histopathologic findings are in complete agreement with those reported by van der Knaap et al.: commensurate decrease of myelin, increased oligodendrocyte density, slight gliosis, sparse phagocytic cells, and axon loss within the central telencephalic white matter. However, in our opinion, the neuropathologic data do not establish a primary axonopathy with secondary myelin disturbance and loss. Thus, if within the cavitory telencephalic white matter loss of axons is obvious, most of the persistent axons are nacked. Those that are still myelinated display abnormally thin myelin sheaths disrupted in places by vacuoles at the ultrastructural level. In addition, at brainstem level, lesions appear acute and recent (loss of myelin sheaths with numerous macrophages containing myelin debris), axons are preserved and naked. Moreover, like van der Knaap et al., we did not observe axon swellings at the optic level, and at the ultrastructural level, the myelinated axons display a preserved cytoskeleton. These observations suggest that myelin sheaths disappear before axon loss and argue in favor of a primary myelin defect giving rise to a secondary axon degeneration.

These different interpretations can be explained by the differences between the clinical courses of our patients and those of van der Knaap et al. Our patients have a short clinical course with terminal bulbar signs, the latter correlated with the acute demyelinating lesions observed in the brainstem. The cases reported by van der Knaap et al., as well as other reported adult cases, have a more protracted clinical course than our cases. This distinct schedule could explain the inability to discern the initial lesions (myelin loss) in the telencephalic white matter from those resulting from a long-standing evolution (axon degeneration). Moreover, the increased number of oligodendrocytes observed in this leukodystrophy argues, in our opinion, in favor of a myelination or myelin maintenance disturbance. Determining whether this oligodendrocyte population represents a primary myelin involvement or a response to myelin loss requires further investigations. We consider that the histologic features reported in this disease suggest a primary myelin involvement and that the leukencephalopathy with vanishing white matter should be considered as a genuine leukodystrophy. Nevertheless, the physiopathogenesis of this syndrome remains unknown and could result from defects intrinsic to oligodendrocytes, environmental factors, or abnormal interactions with glial cells or axons.

Diana Rodriguez, MD, Antoinette Gelot, MD, PhD, Paris, France

Reply from the Authors: We thank Drs. Rodriguez and Gelot for their interesting comments on a newly defined leukencephalopathy, variably called CACH (childhood ataxia with central hypomyelination) and “disease of vanishing white matter.”

Unfortunately, we are not able to evaluate the histologic findings of their cases, as at the time of writing this reply the article referred to has not yet appeared in print. However, Drs. Rodriguez and Gelot state that their findings are in complete agreement with ours providing another piece of evidence that early-onset and later-onset cases are variants of the same disease.

We believe that with the current state of knowledge it is not possible to come to a definitive conclusion about the pathophysiologic of the disease. For this reason we have formulated our conclusion very carefully: “Both magnetic resonance spectroscopy (MRS) and histopathologic findings suggest that it is possible that a primary axonopathy underlies the vanishing of the white matter. We are aware of similar spectroscopic and histopathologic findings in any other known condition, making it impossible to provide definite explanations at this stage.”

We have several reasons for our speculations. MRS of affected white matter in living patients did not show the abnormalities seen as a rule in demyelination (elevated choline and myoinositol) but did show a relative decrease in N-acetylaspartate (neuronal marker). The decrease in N-acetylaspartate was more pronounced in white matter than in cortex, suggesting a greater loss of axons than nerve cell bodies. In addition, MRS of the white matter showed the well-known absolute decrease in the levels of all metabolites, related to the vanishing of all white matter structures.

Histopathology in one adolescent patient showed a commensurate decrease in axons and myelin sheaths in the cerebral white matter, salutary for active demyelination. We did not see a relative sparing of axons as observed by Drs. Rodriguez and Gelot. We found that not only the remaining myelin sheaths but also the remaining axons appeared abnormally thin. Only in the brain-
stem did we find an area of myelin loss with relative sparing of axons. However, the tractlike distribution of the brainstem demyelination closely affecting the ventral tegmental and thalamic 
and central tegmental tracts, and the superior central nuclei, \( t \) suggests an axonal lesion, although the axons appear to be preserved at this stage. Unfortunately, it is often very difficult in suboptimally preserved postmortem brain tissue to distinguish a primary axonal lesion with secondary loss of myelin from a primary myelin lesion with secondary axonal damage. 

We agree with Drs. Rodriguez and Gelot that it is possible that part of the differences in findings may be related to the fact that their autopsy subjects were childhood-onset patients with early death, whereas our cases had a later onset and death. \( t \) It is possible that in later stages of a more protracted disease, axonal loss is more prominent than in earlier stages of a more rapidly progressive disease. Second, it is possible that the primary morphologic focus of the disease is different in different phenotypic variants. For example, childhood X-linked adrenoleukodystrophy is a disease characterized by primary myelin loss, whereas the adult variant adrenomyeloneuropathy is dominated by a spinal axonopathy. \( t \) 

The final conclusion about the pathophysiology of the disease awaits further studies. In this respect, it is important to recognize that, despite significant past and present contributions to understanding of disease mechanisms, classical neuropathologic studies of human patients only can provide a static, often one-time look at the disease process. Conversely, longitudinal examinations of living patients such as repeated MRI and MRS studies have the power to directly study all stages of a disease. Such data can then be combined with neuropathologic investigations, resulting in significant pathogenetic insights. Although it is not possible to come to a definitive conclusion that vanishing white matter is caused by a primary axonopathy, our findings favor this conclusion. Considering our MRS findings, we are convinced that even if the myelin would be primarily affected, the disease process differs from that occurring in the classical leukodystrophies. \( t \) 

M.S. van der Knaap, MD, PhD, W. Kamphorst, MD, PhD, Amsterdam, the Netherlands 

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References 


Cerebral dopamine concentrations during levodopa treatment 

To the Editor: We read with interest the article by Contin et al., describing an application of the “pharmacological effect” compartment analysis to the case of levodopa. A linear transformation of the hysteresis loop of finger tapping rate as a function of the plasma levodopa concentration yielded estimates of half-life for levodopa in the theoretical effect compartment of 1 hour in patients with Hoehn and Yahr stage 3 PD. Similar results have been obtained earlier using the CURS score to calculate effect site concentrations of levodopa. The relationship between the plasma input and the pharmacodynamic effect of a drug is similar to the operation of convolution used for the analysis of dynamic images acquired by PET. We wish to draw several comparisons between the findings of Contin et al. and the results of our compartmental analyses of levodopa kinetics using the dopa decarboxylase substrate \([15 \text{F}]\)fluorodopa (F-dopa). In our constrained physiologic model of F-dopa kinetics, the radioactivity concentrations measured in plasma and in brain by PET are used to estimate clearances and rates for the cerebral metabolism of F-dopa. We obtained estimates for the magnitudes of the unidirectional blood–brain clearance (\( K_{m} = 0.03 \text{ ml/g min}^{-1} \)), the brain–blood elimination rate constant (\( k_{e} = K_{e}/V_{E} = 0.04 \text{ min}^{-1} \)), the relative dopa decarboxylase activity (\( k_{d} = 0.04 \text{ min}^{-1} \)), and the elimination rate constant for decarboxylated metabolites (\( k_{p} = 0.025 \text{ min}^{-1} \)) in putamen of patients with Hoehn and Yahr stage 2 to 3 PD. It is notable that our estimate of \( k_{p} \), which is an index of the half-life of radiotracer dopamine in putamen, is nearly identical in magnitude to the half-life for levodopa in the functional compartment (0.03 min \(^{-1} \)) of patients. Using the above kinetic estimates, and using the concentration curve of levodopa in venous plasma of a patient after oral administration, we calculated the consequent cerebral dopamine concentration as a function of time after levodopa treatment (figure), assuming that this concentration was nil during the off-dopa condition. The calculated dopamine concentration in putamen reached a transient maximum of almost 3 \( \mu \text{M} \) at 90 minutes after levodopa treatment, some 30 minutes after the peak in plasma levodopa concentration. \( t \) The dopamine concentration measured postmortem in putamen of neurologically normal subjects was 40 \( \mu \text{M} \). We conclude that the benefits of levodopa therapy are obtained with cerebral dopamine concentrations far less than normal. The extensive catabolism of dopamine formed from levodopa, \( t \) indicates that the storage of newly synthesized dopamine is incomplete or impaired in patients with PD, consistent with the decline in the functional compartment half-life with increasing Hoehn and Yahr stage. \( t \) Furthermore, the delay to maximal motor response after oral levodopa decreased from 120 minutes to 60 minutes with progression to advanced disease. \( t \) This latter condition may reflect a transition to a disease stage in which the vesicular storage ceases to buffer the extracellular dopamine concentrations in response to plasmin decompositions of levodopa. 

Paul Cumming, PhD, Flemming Hermansen, MD, Albert Gjedde, MD, PhD, Aarhus, Denmark 

Reply from the Authors: We thank Cumming et al. for their interest in our work. We were pleased to see that their findings, obtained by dynamic PET using \([15 \text{F}]\)fluorodopa, \( t \) are in keeping with our levodopa kinetic-dynamic modeling after a levodopa oral.
test. Overall, their data reinforce our suggestion that the search for associations between the results of functional tests by noninvasive clinical measures and that of neuroimaging and pharmacologic processes by PET may be helpful in clarifying mechanisms underlying the progressive degeneration of the nigrostriatal system over time in PD patients.

M. Contin, PharmD, R. Riva, MD, P. Martinelli, MD, P. Cortelli, MD, F. Albani, PharmD, A. Baruzzi, MD, Bologna, Italy

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Pathologic and biochemical studies of juvenile parkinsonism linked to chromosome 6q

To the Editor: Mori et al. describe in detail the clinical and pathologic findings in one parkinsonian patient who had an onset at age 24 and died 38 years later. He improved on a combination of levodopa and bromocriptine. Autopsy showed loss of melanin containing substantia nigra (SN) neurons and gliosis. They detected tau positive neurofibrillary tangles (NFT) mainly in the SN, locus ceruleus (LC), and posterior hypothalamus. Although rare NFT were noted in the cerebral cortex, they concluded that the pathologic picture was not consistent with AD.

I wish to draw attention to our publication of four cases in 1989. All of our patients were white. They each had an early age of onset: 24, 49, 24, and 24 years; and they survived 39, 35, 52, and 47 years, respectively. The clinical profile including response to levodopa was indistinguishable from Lewy body disease, except the survival was exceptionally long. The pathologic findings in our patients were similar to that reported by Mori et al. There were no Lewy body inclusions. Paired helical tau positive NFT were concentrated in SN and LC. After consideration of the clinical and pathologic literature, we concluded that these patients did not fit the profile of any of the known neurofibrillary tangle pathologies, i.e., progressive supranuclear palsy, AD, or postencephalitic parkinsonism. We noted that “a final possibility is that the four patients represent an entity thus far not described.” We concluded that “more investigations are required to clarify further the characteristics of this clinicopathological entity.” We did not conduct genetic studies in those patients, but no family history of similar illness was available. I note that Mori et al. have identified an autosomal recessive form of juvenile PD in one family.

A.H. Rajput, MB, BS, FRCP, Saskatoon, Saskatchewan

Reply from the Authors: We apologize for missing the paper by Dr. Rajput et al. As Dr. Rajput points out, clinical and pathologic features of his four patients are similar to our patient, except that one of his patients had the onset at age 49, slightly older than the upper limit of autosomal recessive juvenile parkinsonism linked to chromosome 6q (6q-linked AR-JP). However, a patient with 6q-linked AR-JP with the age at onset of 58 years has been reported outside of Japan. Thus, there is still a possibility that his patients have apparently sporadic 6q-linked AR-JP. According to our experience, apparently sporadic patients who have a mutation in the parkin gene exist, although the number is small.

An interesting question is whether NFT are a characteristic feature of 6q-linked AR-JP. Two other autopsy cases of 6q-linked AR-JP have been published so far, and these two cases did not show NFT, but apparently the more sensitive staining for NFT, such as Gallyas-Braak stain or immunohistochemistry for tau, were used in their reports. The disease duration in our patient reported in Neurology was 38 years; that reported by Takahashi et al. was 57 years, and that reported by Yamamura et al. was 33 years. Therefore, disease duration has nothing to do with the formation of NFT. This question will be clarified by gene analysis and immunohistochemical studies using an antibody against parkin protein on pathological specimens reported by Rajput et al. Both of these studies can be conducted in our laboratories. We are very happy to perform collaborative studies to see whether their patients had 6q-linked AR-JP.

Finally, there is still a small possibility that their patients had a postencephalitic type of parkinsonism without an attack of encephalitis. Such cases have been reported.

Hideo Mori, MD, Tokyo, Japan

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References


Wallerian degeneration of the pyramidal tract does not affect stroke rehabilitation outcome

To the Editor: The article by Miyai et al. points out that the residual pyramidal tract contributes little to stroke recovery. Although their study comprised a large number of patients, its design casts doubts on this conclusion. 1) The authors did not study specifically the function of motor cortex and its pyramidal (corticospinal) tract but used scores composed of functionally different subitems. Motor cortex mediates the exertion of muscle force and of individual finger movements. 2) They did not assess the viability of the corticospinal transcallosal and transcallosal magnetic stimulation (TMS), which is known to predict recovery from hemiparetic stroke. 3) They did not use anatomic information to localize the corticospinal tract in their MRIs. This concern is evident from the figure in their article that shows that the infarct damaged the rostral part of the paraventricular white matter and the knee area of the internal capsule. In contrast, the more posterior portion of the internal capsule that has been shown by anatomic tracing to accommodate the corticospinal tract was spared. Nevertheless, Miyai et al. successfully demonstrated Wallerian degeneration (WD) in descending tracts that pass the internal capsule but do not exclusively contribute to the corticospinal tract. The authors assessed only quantitatively whether WD was present. They did not use the gray scale for assessing the amount of WD that precluded a straightforward correlation with clinical scores.

Recently, we assessed the integrity of the corticospinal tract by a clinical score, electrophysiologically by TMS, and morphometri-
cally using stereotaxis atlas information in patients with first hemiparetic stroke. We showed that the degree of involvement of the corticospinal tract provided an indication for the motor impairment in the first 72 hours after stroke and for motor recovery 30 days. These data agree with the finding that WD significantly lengthened the patients’ stay in hospital and that there was a significant effect for WD to account for this observation as reported by Miyai et al.2 The authors did not state how long after infarction the first scoring of the patients was performed.

Cerebral plasticity underlying functional recovery in brain damage is a focus of current neuroscience research. The involved mechanisms are multifocal.4 For example, similar to the findings of others who studied patients with a long interval of 5 to 96 months after infarction,5 we observed that an affection of the thalamus contributed to hemiparesis.5 Further, functional neuroimaging did not simply show complex changes in the damaged and undamaged cerebral hemisphere related to motor recovery,6 but also showed specific activations adjacent to the infarction suggesting recruitment of spared parts of motor and premotor cortex and their corticospinal projections.4,9 In agreement with functional neuroimaging data, we and others7–9 have shown that the main recovery mechanism from hemiparesis is the preservation of integrity of the corticospinal tract.

Rüdiger J. Seitz, MD, Ferdinand Binkofski, MD, Düsseldorf, Germany

Reply from the Authors: Drs. Seitz and Binkofski raise several important points for future research on outcomes after stroke, as clinical functional recovery reflects cerebral plasticity. First, we did not intend to convey the conclusion that damage to “...the residual pyramidal tract contributes little to stroke recovery.” Our data demonstrated that WD of the pyramidal tract, as detected by MRI, did not affect rehabilitation outcome as assessed by the Functional Independence Measure and the Stroke Impairment Assessment Set (SIAS). In fact, individual finger movements were assessed as part of the SIAS, and there were no differences, similar to the findings for the other muscle groups of the paralyzed upper extremity. The details of the SIAS have been published,11,12 but we should have stated these results explicitly. We defer to Seitz’ and Binkofski’s experience with TMS,5,7 and with them we emphasize the concordance of their findings with our report that showed significantly longer rehabilitation hospital stay in the group with WD. We agree that the timing of the appearance of MR signal thought to reflect WD and the precise structure–function correlation are important issues, and our data are currently undergoing that systematic analysis. This ongoing analysis should bring about discrete evaluation measures that will reflect maturing pathology after the initial stroke injury.

Ichiro Miyai, MD, PhD, Tsunehiko Suzuki, MD, PhD, Kisou Kubota, MD, PhD, Osaka, Japan

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Chronic "brain death": meta-analysis and conceptual consequences
Antonio López-Navidad
*Neurology* 1999;53;1369

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