Alzheimer's Disease and Transmissible Virus Dementia (Creutzfeldt-Jakob Disease)

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INTRODUCTION

THE DISCOVERY that two chronic degenerative diseases of the central nervous system, kuru and Creutzfeldt-Jakob disease (CJD), could be transmitted to nonhuman primates after inordinately long incubation periods from filtered suspensions of diseased brain tissue[1,2], provided a strong impetus to the search for a viral origin of other chronic brain diseases of unknown etiology. Alzheimer's disease (AD) has received particular attention in view of its many similarities to CJD, summarized in TABLE 1, and in this paper we shall present the case for considering AD as a possible viral dementia.

CLINICAL COMPARISONS

Both AD and CJD are presenile dementias that affect males and females with equal frequency. In two recently published case series,[3,4] shown in TABLE 2, age at onset frequency distributions were remarkedly similar, ranging between 40 and 89 years of age for AD (average 67 years), and between 35 and 84 years of age for CJD (average 60 years). Occasional familial cases of both AD and CJD (and also sporadic cases of CJD) have been documented in younger individuals.[5-8] Although the duration of AD is usually much longer than that of CJD (8 years versus 8 months),

0077-8923/82/0396-0131 $01.75/0

TABLE 1

COMPARISONS BETWEEN ALZHEIMER'S DISEASE AND SPONGIFORM VIRUS ENCEPHALOPATHIES

Clinical Comparisons (AD and CJD)
Presenile dementias with similar age at onset distribution curves.
Males and females equally affected.
Subacute to chronic course with overlapping durations of illness.
Presence of myoclonus and periodic EEG (usual in CJD, occasional in AD).
Familial occurrence in 10–15% of cases, with autosomal dominant pattern of inheritance.
Coexistence of AD and CJD within families.
Coexistence (?) of AD and CJD in the same individual.
Conjugal occurrence.
Pathologic Comparisons
Morphologic spectrum overlaps in AD, CJD, kuru, scrapie.
Amyloid plaques in most AD and kuru, occasionally in CJD.
Spongiform change in most CJD, occasionally in AD.
Biologic Comparisons
Plaque-producing strains of experimental scrapie in mice.
Paired helical filament (PHF) "assembly factor" in AD brain, "scrapie-associated fibrils" (SAF) in synaptomsomal fractions of scrapie brain.
Decreased choline acetyltransferase in AD and scrapie.
Induction of *in vitro* cell fusion in 66% of CJD, 59% of familial AD.
Transmissibility
Primary transmission of spongiform encephalopathy to primates from 70% of CJD, 95% of kuru, 80–100% of scrapie, 4% (?) of AD.

there is nevertheless considerable overlap, with some cases of AD dying as early as several months after onset, and some cases of CJD living as long as 10 years.[4,5,9-11]

AD typically presents as a progressive mental deterioration, with an insidious onset consisting of subtle signs of memory loss, often associated with behavioral and speech disturbances. As the disease evolves, there occurs an increasing disruption of higher cortical functions, progressing to complete disorientation and reducing speech to isolated words and phrases, or to a state of mutism. Various primitive reflexes can be elicited, movements become stereotyped, and an extrapyramidal type of rigidity is often observed in the late stage of the disease.

CJD also presents as a progressive mental deterioration, but which from an early stage is usually associated with one or more neurologic ab-

TABLE 2
AGE AT ONSET DISTRIBUTIONS OF ALZHEIMER'S DISEASE AND CREUTZFELDT-JAKOB DISEASE

Age Group (years)	Number of Cases	
	Alzheimer's Disease*	Creutzfeldt-Jakob Disease†
35–39	0	4
40–44	1	4
45–49	2	8
50–54	9	11
55–59	17	23
60–64	19	30
65–69	27	24
70–74	25	18
75–79	11	1
80–84	12	1
85–89	2	0
Total	125	124

* Data from Heston *et al.*[3]
† Data from Brown *et al.*[4]

normalities, including cerebellar, visual, pyramidal, and extrapyramidal signs. Myoclonus, with or without other types of movement disorders, occurs relatively late in the course of illness in nearly 90 percent of patients. The EEG is also invariably abnormal in the later stages of disease, often showing periodic bursts of slow waves, or at some point in over half the patients, a characteristic pattern of nearly regular high-voltage spikes at a frequency of 1-2 cycles per second.

Exceptions to these "typical" clinical evolutions are, however, not uncommon. On the one hand, patients with CJD may show little more than a slowly progressive disturbance of mentation and behavior until rather late in their illness (particularly in those cases of longest duration), abnormal movements may be minimal, and the EEG may show only nonspecific generalized slowing.[4,11,12] On the other hand, patients with AD may experience severe and varied neurologic abnormalities in association with dementia during the course of their illness, including myoclonus and an EEG tracing indistinguishable from the "characteristic" pattern of CJD.[5,10,13-20] In short, there occurs enough of a clinical "grey zone" in the symptomatology and clinical evolution of the two diseases

to make it difficult to differentiate AD from CJD in their earlier stages, and sometimes to cause diagnostic uncertainty throughout the duration of illness.

PATHOLOGIC COMPARISONS

Indeed, even neuropathologic examination will not always provide a definitive diagnosis. Neuronal loss and gliosis are common to both diseases. Senile plaques and neurofibrillary tangles, which comprise the histologic basis of AD, are sometimes present as well in CJD.[15,21] and conversely, spongiform change, which is the pathologic hallmark of CJD (but which may at times be so minimal as to go undetected by conventional light microscopy), is occasionally seen in brains from patients with AD.[15,22,23] An unusually well-studied, recently reported case will serve to illustrate the problem.[24] A 43-year-old man with a 4-year history of slowly progressive dementia underwent a brain biopsy that confirmed the clinical impression of AD, but he then deteriorated rapidly, developed myoclonus and a periodic EEG, and on repeat biopsy showed the typical spongiform change of CJD. Subsequently, autopsy examination confirmed the combined histologic changes of both AD and CJD, with senile plaques and neurofibrillary tangles as well as spongiform change. Since brain tissue from this patient inoculated into primates has failed to transmit disease, and since the patient's brother subsequently died of uncomplicated, histologically verified AD, it remains unclear whether the patient himself had only a very unusual clinical and pathologic picture of AD, or coexisting AD and CJD.

The combination of spongiform change and plaques is characteristic of kuru, and although uncommon, plaques have been found in brains from sheep with naturally occurring scrapie.[25] The morphologic characteristics of AD, CJD, kuru, and scrapie are thus interlaced in a virtually complete spectrum of shared neuropathology.

GENETIC COMPARISONS

Approximately 10–15 percent of cases of both AD and CJD occur in families in which at least one other member is also affected with the same disease, and the proportion of affected to total members of each generation in the combined family populations, as well as the study of certain individual families, indicates an autosomal dominant pattern of inheritance.[5,26,27] Recent study of a series of 52 families with AD[5] revealed

that a surprisingly large number (almost one-third) of the affected members in 17 of the families had a relatively rapid progression of dementia accompanied by myoclonus or other abnormal movements, pyramidal, extrapyramidal, or cerebellar signs, or periodic sharp wave complexes in the EEG, which in the absence of autopsy examination might have led to the clinical diagnosis of CJD. Even more intriguing was the finding that in four AD families, one member had a pathologically confirmed spongiform encephalopathy characteristic of CJD.

The converse situation of CJD families including a single member with AD, or families having one member with CJD and another member with AD has not been described, although there is one recorded instance of a wife with CJD whose husband was almost simultaneously ill with AD, both cases having been pathologically verified.[5] Concordant and monozygotic discordant twins have been reported in AD,[5,28-30] as well as a single case of CJD in dizygotic twins, with the surviving twin still in good health at age 58.[31]

BIOLOGIC COMPARISONS

Although plaques are never seen in the experimental form of CJD and kuru, even on primary transmission to primates, they may occur as a major histologic feature of certain mouse-virus strain combinations of experimental scrapie.[32] Recent evidence suggests that the plaques in experimental scrapie are a direct effect of the infective agent,[33] and the morphologic variety and evolution of such plaques appear to be similar to what is seen in AD[34,35]

Abnormal fibrillary structures, or "scrapie-associated fibrils" (SAF) have also been observed by electron microscopy in subfractions of synaptosomal preparations from brains of scrapie-affected mice and hamsters, although they have not been found on electron-microscopic examination of the brains themselves.[36] They are morphologically dissimilar to normal brain fibrils, but do bear a resemblance to amyloid, including the type of amyloid present in plaques from patients with AD.

SAF appear, however, to be different from the structures interpreted as paired helical filaments (PHF) observed in human fetal neuron cultures inoculated with AD brain extracts or spinal fluid.[37] These latter filaments, induced by a so-called PHF "assembly factor" that passes through a 250 nm filter, sediments between 40S and 80S, and is sensitive to both heat and ultraviolet irradiation, are in turn not morphologically identical to the PHF in neurofibrillary tangles in AD brain.

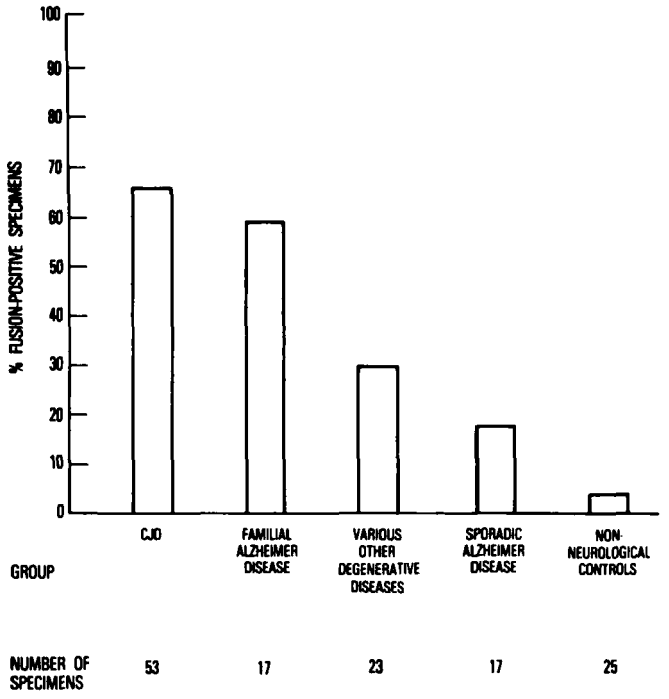

FIGURE 1. Comparison of frequency of *in vitro* cell fusion induced by 10% saline brain suspensions from patients dying from CJD, AD, and various other neurologic and non-neurologic diseases.[20]

The significance of these experimentally induced plaques and filamentous structures to the pathogenesis of amyloid plaques and neurofibrillary tangles in naturally occurring AD remains problematic and subject to continuing research.

Two further points of biologic comparison between AD and spongiform virus encephalopathies do not depend on morphologic studies, but are not thereby less difficult to assess. Quantitative assay of the enzyme choline acetyltransferase necessary for cholinergic neurotransmission has revealed subnormal levels in brain tissue both from patients with AD and from scrapie-infected animals.[38,39] It is not clear whether this decrease is due to a common pathogenetic mechanism or is merely a relatively nonspecific biochemical consequence of serious degenerative neuropathology.

Finally, there is the interesting observation, shown in FIGURE 1, that

brain suspensions from patients with familial (but not sporadic) AD contain a factor that induces *in vitro* cellular fusion at nearly the same high frequency as CJD and scrapie brain suspensions.[20] Lack of specificity is once again a major concern, since cell fusion was also induced by a smaller proportion of brains from patients with other neurologic diseases, and even a rare nonneurologic control. Whatever its cause, the induction of *in vitro* cell fusion represents the first laboratory measurement of a biologic distinction between sporadic and familial AD, and yet another possible link between AD and the spongiform virus encephalopathies.

TRANSMISSIBILITY

Primary transmission of CJD has been accomplished in 70 percent of over 300 patients in whom the diagnosis was suspected, from suspensions of brain tissue inoculated intracerebrally into primates (as of June 1982), and this high level of success has been equalled or exceeded in primary transmissions to primates from patients with kuru, and in primary transmissions to mice from sheep affected with scrapie.[40,41]

The contrast between transmissibility of these diseases and AD is disappointing, as shown in TABLE 3. Specimens from a total of 97 patients with either the familial or sporadic form of AD have now been inoculated into primates. Excluding the 9 "suboptimal" negative inocula (brain tissue culture explants, formalin-fixed brain, or nonneural tissues), 8 "inconclusive" inoculations in animals that died early of intercurrent illnesses, and the 21 most recently inoculated specimens still on test, there remain 57 patients who may be classified as negative by the criterion of inoculated animals failing to develop neurologic disease after a duration exceeding by two standard deviations the average incubation period of CJD. In viewing these transmission attempts as negative, however, it must be recalled that incubation periods have in some cases extended beyond 6 years; that transmission may occur without illness, being demonstrable only by neuropathologic examination; and that, furthermore, the existence of marked strain differences between various CJD virus isolates from human brains, with very different host ranges in transmission experiments, leaves open the possibility that species thus far employed in transmission attempts with AD tissues have been inappropriate hosts.[42,43]

Inocula from two patients transmitted a spongiform encephalopathy that was clinically and pathologically characteristic of CJD, and not AD.

TABLE 3
ATTEMPTS TO TRANSMIT ALZHEIMER'S DISEASE TO NON-HUMAN PRIMATES*

	Familial Alzheimer's Disease	Sporadic Alzheimer's Disease
Positives (unverified)†	2	0
Negatives‡	12	45
Suboptimal inocula (negative)§	4	5
Early death (inconclusive)¶	2	6
On test‖	8	13
Total patients inoculated	28	69

* Results through June 1982. Except as noted, all inocula were supernatants from 2000 rpm centrifuged 1-20% ground brain suspensions, given as 0.1-0.3 ml intracerebral inoculations. Most specimens were inoculated into at least two animals.

† See TABLE 3 and text for details.

‡ Animals alive and well, or dead without clinical or pathologic signs of disease, after a duration of more than the mean (plus 2 SD) incubation period of experimental Creutzfeldt-Jakob disease in the primate species inoculated.

§ Includes specimens of liver, urine, sputum, formal-fixed brain, and tissue culture fluid from brain explant cultures.

¶ Animals died without clinical or pathologic signs of disease after a duration less than the mean (plus 2 SD) incubation period of experimental Creutzfeldt-Jakob disease in the primate species inoculated.

‖ Animals alive and well after a duration less than the mean (plus 2 SD) incubation period of experimental Creutzfeldt-Jakob disease in the primate species inoculated.

Details of these two transmissions, updated through June 1982 from a previous report based on results through September 1979,[44] are presented in TABLE 4. The first patient, A. Yo, was a member of an AD family, and pathologically verified brain tissue from an affected sister has not transmitted disease to primates. However, one of three animals inoculated in 1968 with the patient's brain tissue and a pool of visceral tissues died with a spongiform encephalopathy. Brain tissue from the affected animal was subsequently passaged serially in primates, and neuropathologic examinations consistently showed neuronal loss, gliosis, and spongiform change, without plaques or neurofibrillary tangles. In 1973, another pair of animals was inoculated, both of which died of nonneurologic illness sufficiently long after inoculation to be considered as negative. In 1975, an additional large group of animals was inoculated with the same original brain suspension: one of them died of a

TABLE 4

CASES OF ALZHEIMER'S DISEASE INOCULATED INTO NON-HUMAN PRIMATES WITH TRANSMISSION OF A SPONGIFORM ENCEPHALOPATHY*

Patient	Inoculum Source†	Primate Host	Route of Inoculation‡	Date of Inoculation	Duration (months)	Neuro-pathology
A.Yo.	Brain + LSHK	Chimpanzee	ic,iv,sc§	1968	166	
	Brain + LSHK	Squirrel	ic,iv,sc§	1968	23 (died)	Pos
	Brain + LSHK	Cynomolgous	ic,iv,sc§	1968	30 (died)¶	Neg
	Brain	Squirrel	ic,iv	1973	46 (died)¶	Neg
	Brain	Squirrel	ic,iv	1973	52 (died)¶	Neg
	Brain	Chimpanzee	ic,iv	1975	84	
	Brain	Afr. Green	ic,iv	1975	88	
	Brain	Afr. Green	ic,iv	1975	88	
	Brain	Cynomolgous	ic,iv	1975	88	
	Brain	Cynomolgous	ic,iv	1975	88	
	Brain	Rhesus	ic,iv	1975	88	
	Brain	Capuchin	ic,iv	1975	88	
	Brain	Capuchin	ic,iv	1975	88	
	Brain	Spider	ic,iv	1975	61 (died)¶	Neg
	Brain	Spider	ic,iv	1975	88	
	Brain	Squirrel	ic,iv	1975	88	
B.Ha.	Brain bx	Squirrel	ic,iv	1972	29 (died)	Pos
	Brain bx	Capuchin	ic,iv	1972	40 (died)	Pos
	Brain bx	Chimpanzee	ic,iv	1975	61 (died)¶	Neg
	Brain bx	Capuchin	ic	1975	33 (died)¶	Neg
	Brain bx	Squirrel	ic	1975	83	
	Urine	Capuchin	ic	1976	42 (died)¶	Neg
	Urine	Squirrel	ic	1976	70	
	Feces	Squirrel	ic	1976	70	
	Saliva	Squirrel	ic	1976	70	

* Modified and updated through June 1982 from Table 4 of Goudsmit *et al.*[44] Five animals dying of nonneurologic intercurrent illnesses less than 1 year after inoculation are not included in the table. † LSHK-liver, spleen, heart, kidney. ‡ ic-intracerebral, iv-intravenous, sc-subcutaneous. All inocula were supernates from 2000 rpm centrifuged 10% ground tissue suspensions. § Inoculated ic and iv with brain suspension and sc with a pool of the visceral suspensions. ¶ Nonneurologic illness.

nonneurologic illness, and all others remain alive and healthy well beyond the average incubation period of experimentally transmitted CJD. Additionally, cats, goats, and guinea pigs have also been inoculated without transmission of disease. No further inoculations are planned, and, barring the chance occurrence of an extremely long incubation period in animals still under observation, the transmissible nature of this case must be considered unverifiable.

The second patient, B.Ha., is also a member of a (probable) AD family, her father having died with a clinically similar, but pathologically unverified, disease. After an approximately 10-month course of slowly progressing dementia, she had a brain biopsy that showed the typical pathology of AD. Both animals inoculated in 1972 with this biopsy specimen died with a spongiform encephalopathy typical of CJD, without plaques or neurofibrillary tangles. In 1975, three further animals were inoculated with a newly prepared suspension of the original brain biopsy: two died of nonneurologic illnesses after an interval longer than the average incubation period of CJD, and the third remains alive and well. Urine, feces, and saliva inoculated into four additional animals in 1976 have not transmitted disease. Very recently, the patient died after a 12-year illness that was entirely consistent with the clinical and biopsy diagnosis of AD, and although the brain has not yet been examined histologically, frozen tissue has already been inoculated into cats, monkeys, and a chimpanzee. This patient thus presents us with a unique opportunity to confirm by necropsy material an as yet unverified biospy transmission of AD.

SUMMARY

Ample justification exists on clinical, pathologic, and biologic grounds for considering a similar pathogenesis for AD and the spongiform virus encephalopathies. However, the crux of the comparison rests squarely on results of attempts to transmit AD to experimental animals, and these results have not as yet validated a common etiology. Investigations of the biologic similarities between AD and the spongiform virus encephalopathies proceed in several laboratories, and our own observation of inoculated animals will be continued in the hope that incubation periods for AD may be even longer than those of CJD.

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