Clinical Presentation

Creutzfeldt-Jakob Disease

Subacute Spongiform Encephalopathy

(Prionopathies)

Lawrence S. Honig, MD, PhD

Taub Institute for Research, G. H. Sergievsky Center,
Department of Neurology, and The Neurological Institute

Columbia University College of Physicians and Surgeons

Prion Diseases by Pathogenetic Mechanism

- **Idiopathic** – sCJD, variants: ataxic, visual, sFI
- **Genetic** –
  - Familial CJD (fCJD)
  - Gerstmann-Straüssler-Scheinker Syndrome (GSS)
  - Fatal familial insomnia (FFI)
- **Transmissible** –
  - Iatrogenic CJD (iCJD)
  - Kuru
  - New variant CJD (vCJD)

Clinical Diagnosis of CJD

- Typically age 50-75 (range 23-97, median 68)
- **Rapidly progressive dementia**
- **Myoclonus** (and startle myoclonus)
- **Ataxia**
- Weakness, parkinsonism, speech change
- Cortical visual dysfunction (blindness/hallucinations)
- **EEG findings**
- **CSF findings**
- **MRI findings**

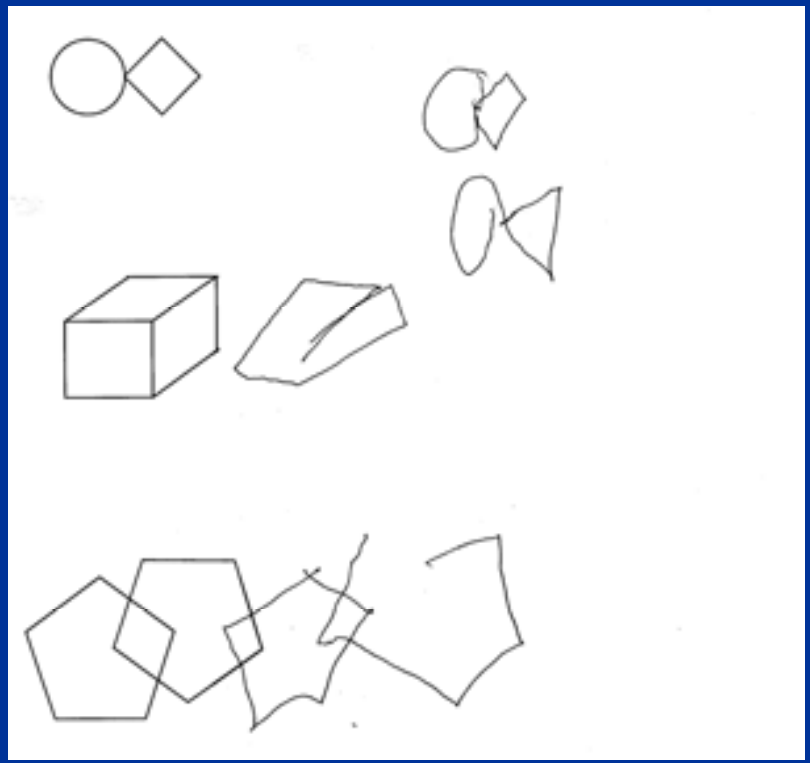
Clinical Stages of CJD

- Insidious cognitive change
  - focal cortical signs in memory, language, visuospatial function, praxis, behavior
- Progressive motor abnormalities
  - ataxia, bilateral rigidity, hyperreflexia, Babinski signs, myoclonus, startle
- Terminal stage
  - increasing dementia, rigidity, paralysis
- Death
  - typically from aspiration (or decubitus ulcers or urosepsis)

Clinical Signs in sCJD

SIGN	FREQUENCY*
	%
Cognitive deficits (dementia), including psychiatric and behavioral abnormalities	100
Myoclonus	>80
Pyramidal tract signs	>50
Cerebellar signs	>50
Extrapyramidal signs	>50
Cortical visual deficits	>20
Abnormal extraocular movements	>20
Lower-motor-neuron signs	<20
Vestibular dysfunction	<20
Seizures	<20
Sensory deficits	<20
Autonomic abnormalities	<20

*Data are from the United States,[15] the United Kingdom,[33] and France.[34]



Copied Drawings of a CJD Patient

RT Johnson & CJ Gibbs, New Engl J Med, 1998

Progression of Dementia

- Typically first signs are very subtle
  - slowness, fatigue, insomnia, inattention, confusion
  - personality change, depression, hallucinations
  - language, memory, perceptual change
- Functional change may occur
  - Loss of interests, loss of modesty, car accidents
- Total duration often less than 6 months
- Marked “snowballing”: patients may progress to stupor/coma during hospital evaluation

Dementia with Rapid Progression

- Chronic illness with apparent rapid acceleration
  - History not correctly provided
  - Precipitating event causing appearance of rapid decline (e.g. loss of partner or support)
  - Concomitant medical illness causing decline (e.g. dehydration, infection, stroke, cancer, anemia)
- Other acute encephalopathies or encephalitides
  - rabies, HSV, HIV, Hashimoto's, carcinomatous, paraneoplastic, toxic encephalopathies

Non-CJD Dementias with Myoclonus

- Acute encephalitides (e.g. HSVE)
- Lewy Body Dementia
- Corticobasal degeneration
- Frontotemporal dementia (e.g. FTD-ALS)
- Drug effects
- Epileptic disorders
- Alzheimer's disease (late)

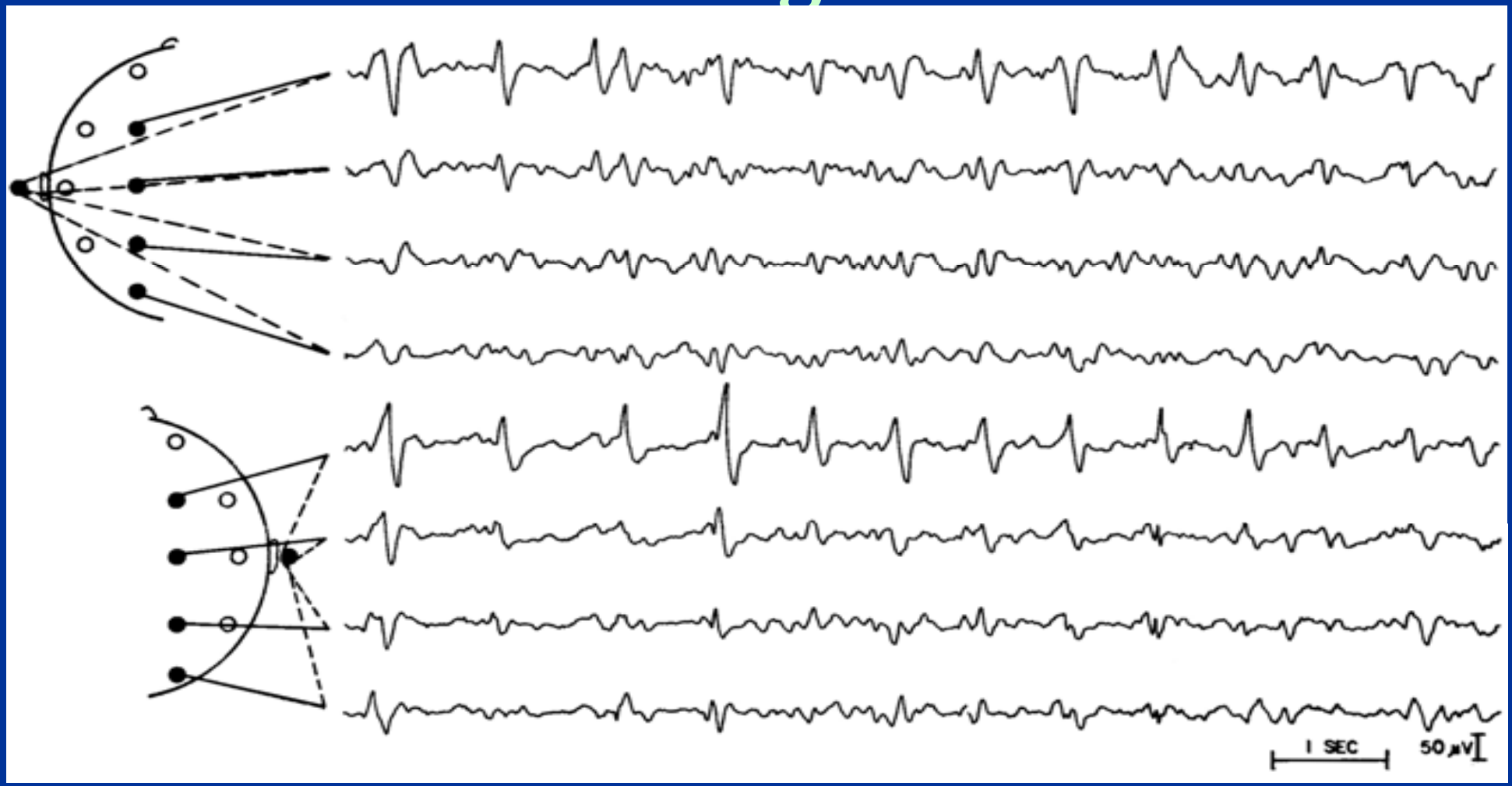
Other Causes of Ataxia in Dementia

- Concomitant spinal disorder (spinal stenosis)
- Concomitant neuropathic disorder
- Hydrocephalus
- Alcoholic degeneration
- Orthopedic disease (hip arthritis)
- Alzheimer's disease (late)
- Parkinsonian disorders

EEG: Periodic Sharp Wave Complexes

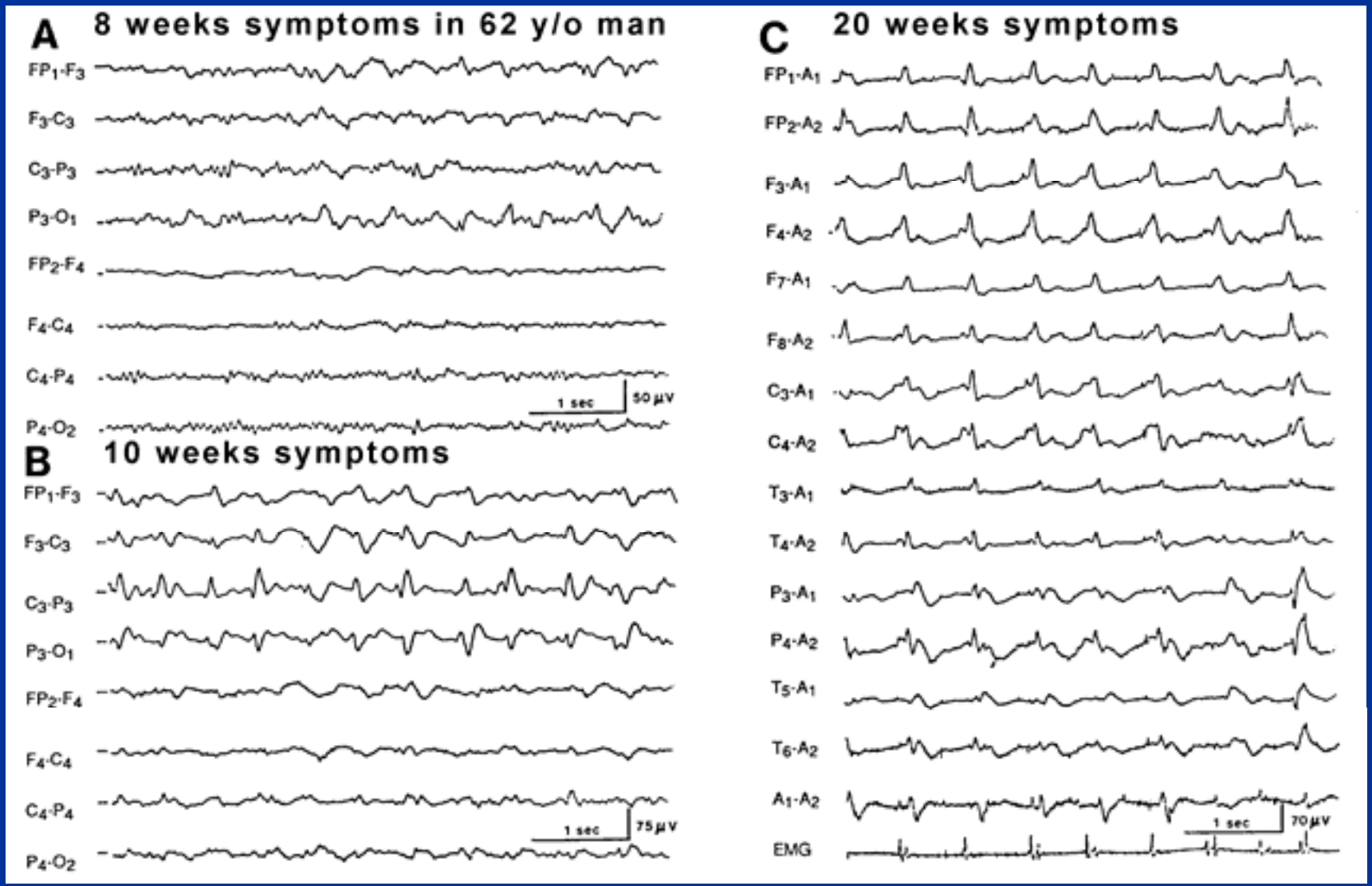
- Periodicity about 1 Hz (0.5 – 2 Hz; 500 – 2000 msec)
- Stereotyped sharp triphasic/diphasic complex
- Duration 100 – 500 msec
- Usually frontally (anteriorly) – dominant
- Typically symmetric, may be asymmetric/unilateral
- Often more prominent while awake (sometimes not)
- Background typically abnormal, disorganized, slow
- Complexes sometimes time-locked to myoclonus
- Pattern evolves: decreased amplitude, ?longer period
- Pattern prevalence: up to ~70 –90% of sCJD cases

EEG Findings in CJD



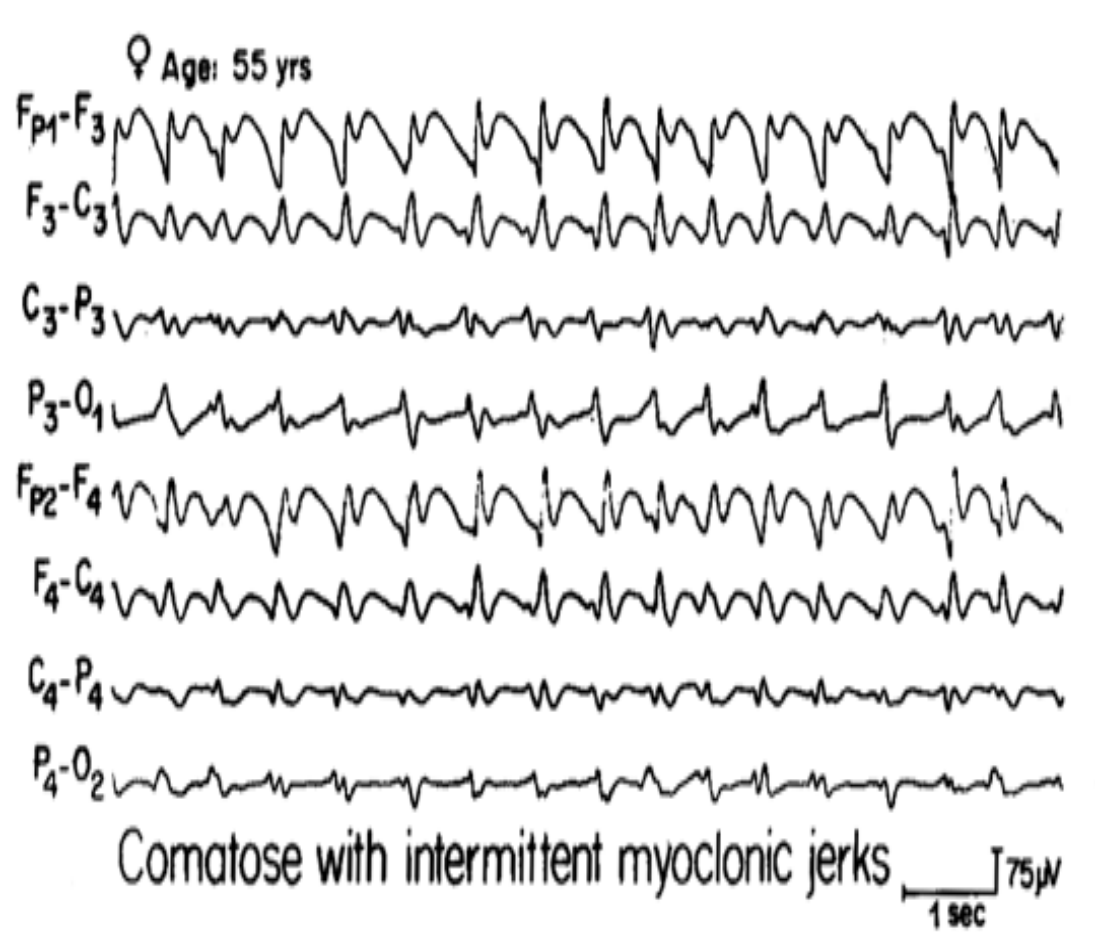
83 y/o 5 mos confusion, dressing apraxia, L VF spatial distortion, startle then spontaneous myoclonus, expired 3 wks p EEG (R Spehlman, EEG Primer, 1st Ed., Elsevier: Amsterdam, 1981)

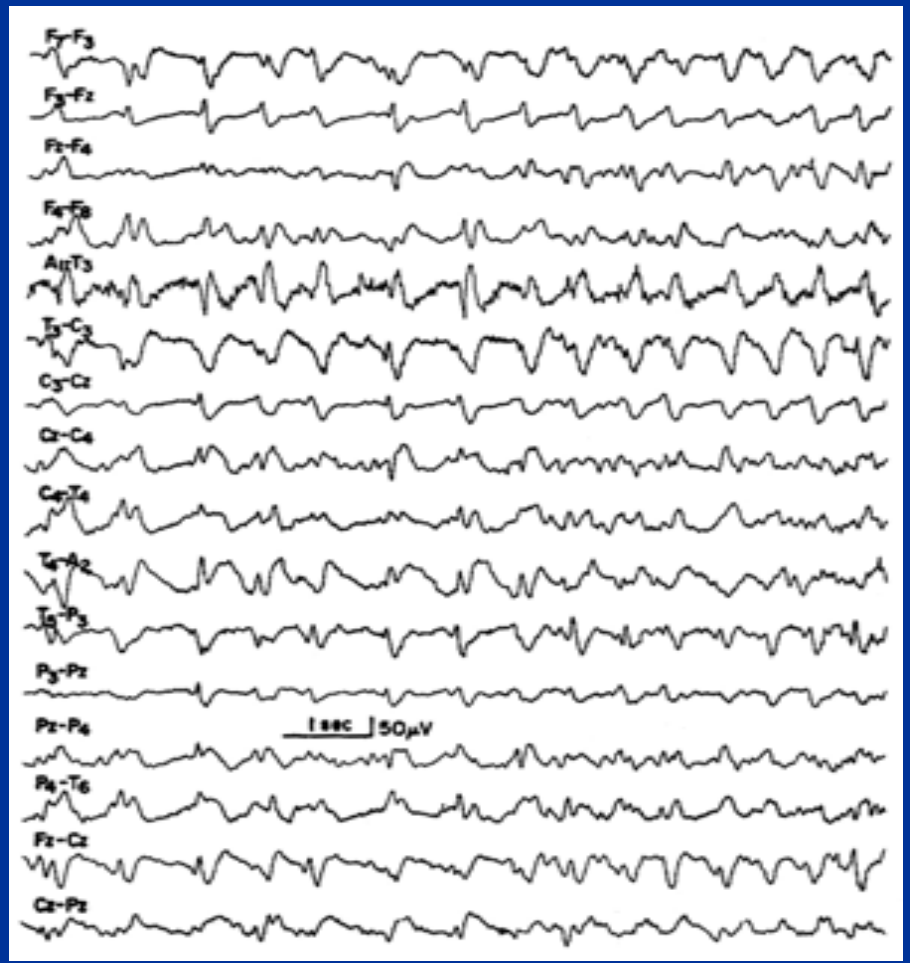
CJD: Progression of EEG Changes



O Markand, in DD Daly & TA Pedley, Current practice of clinical electroencephalography, Raven: NY 1990)

Other Examples of EEG Patterns in CJD

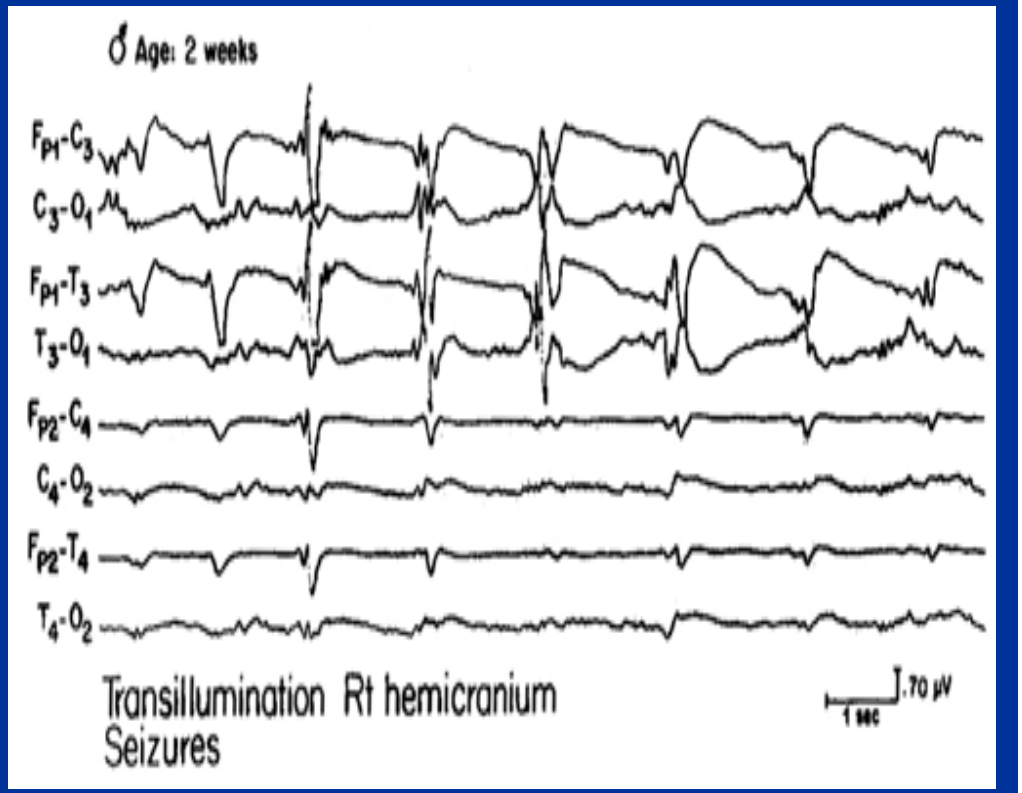


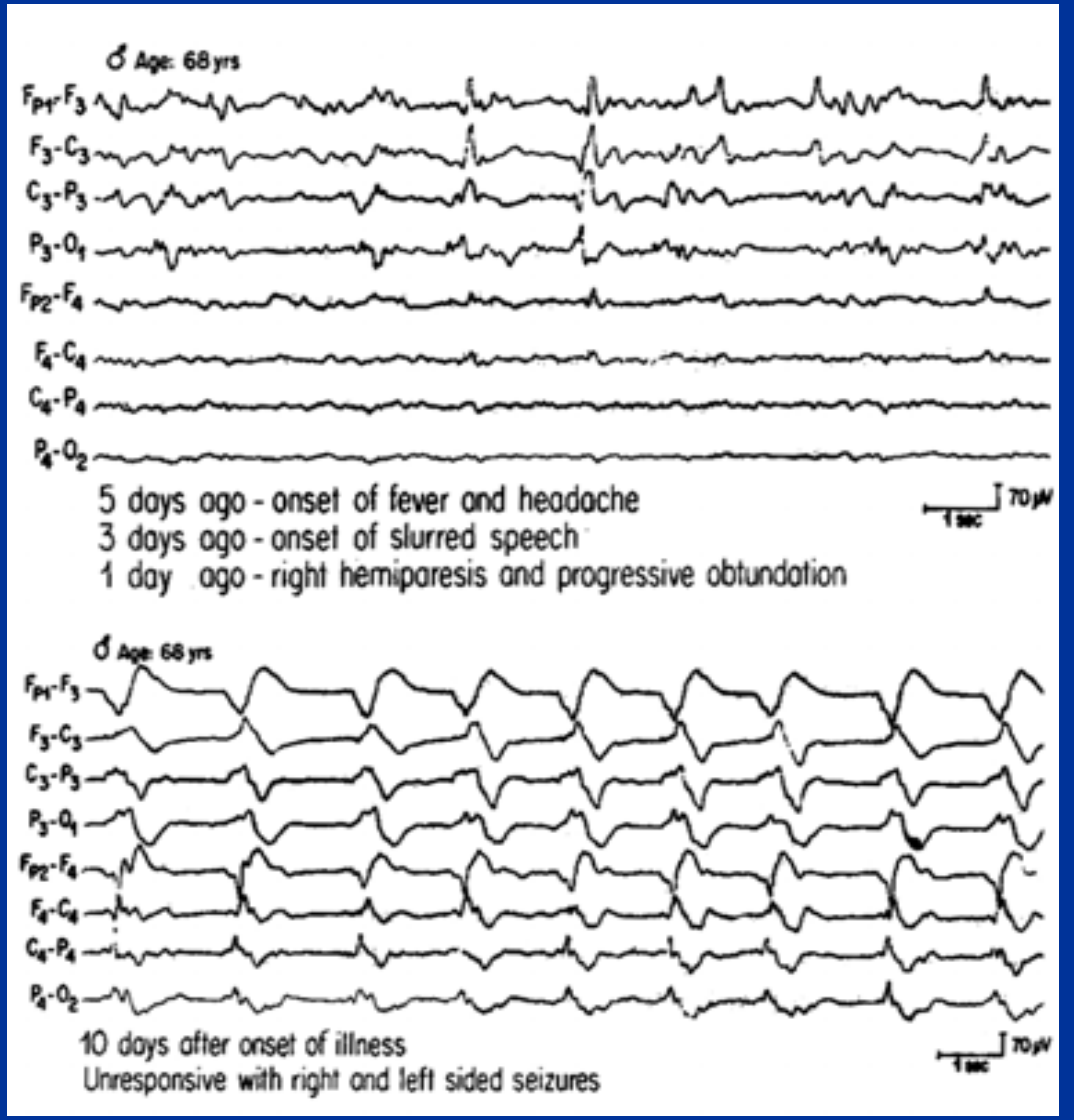


E Niedermayer & F Lopes da Silva, Electroencephalography, Williams & Wilkins: NY, 1987

EEG is Nonspecific

Similar patterns occur in HSVE, anoxic encephalopathy, etc.





E Niedermayer & F Lopes da Silva, Electroencephalography, Williams & Wilkins: NY, 1987

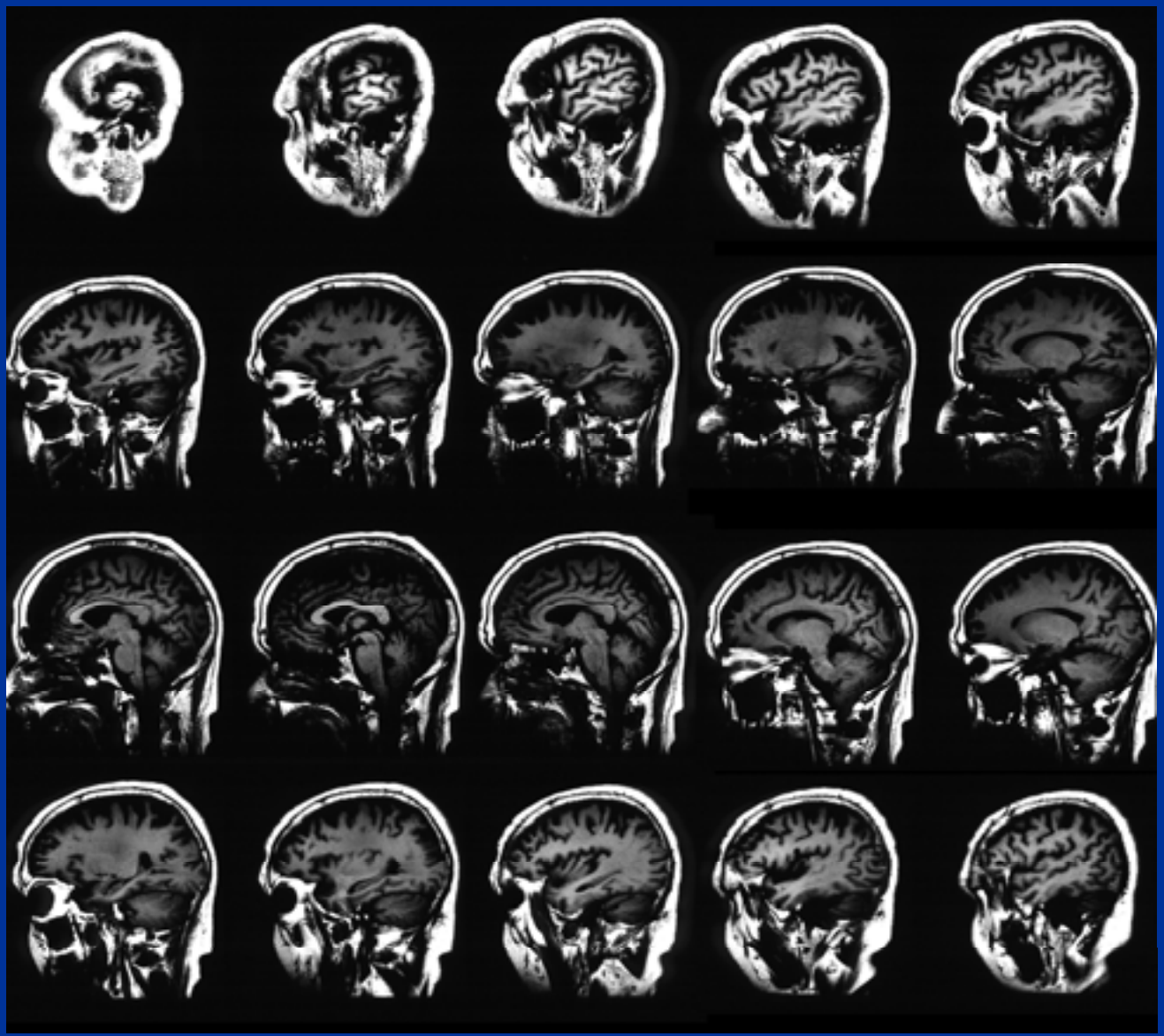
Lumbar Puncture
Cerebrospinal Fluid Analysis

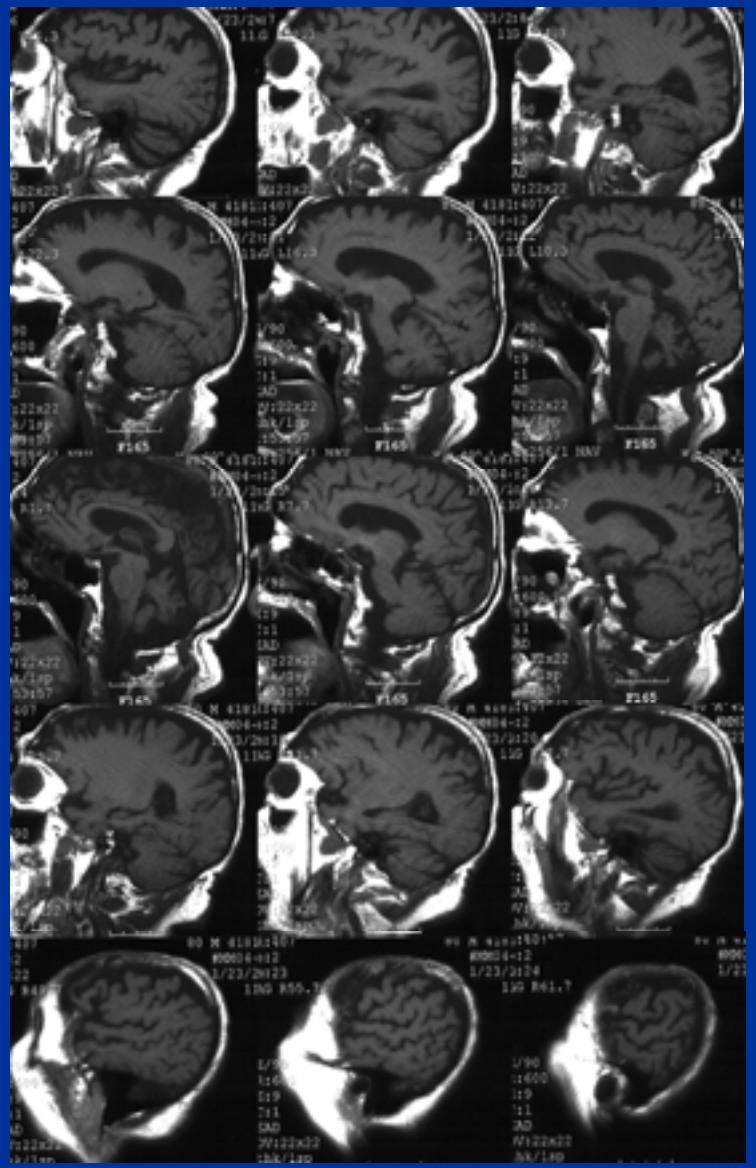
- Usually no significant cellular response
- Often mildly elevated total protein
- Elevated ***14-3-3*** protein (WB, ELISA)
- Elevated ***tau*** protein (ELISA)
- Elevated ***NSE*** protein (ELISA)
- Elevated ***S100*** protein (ELISA)

MRI Findings in CJD

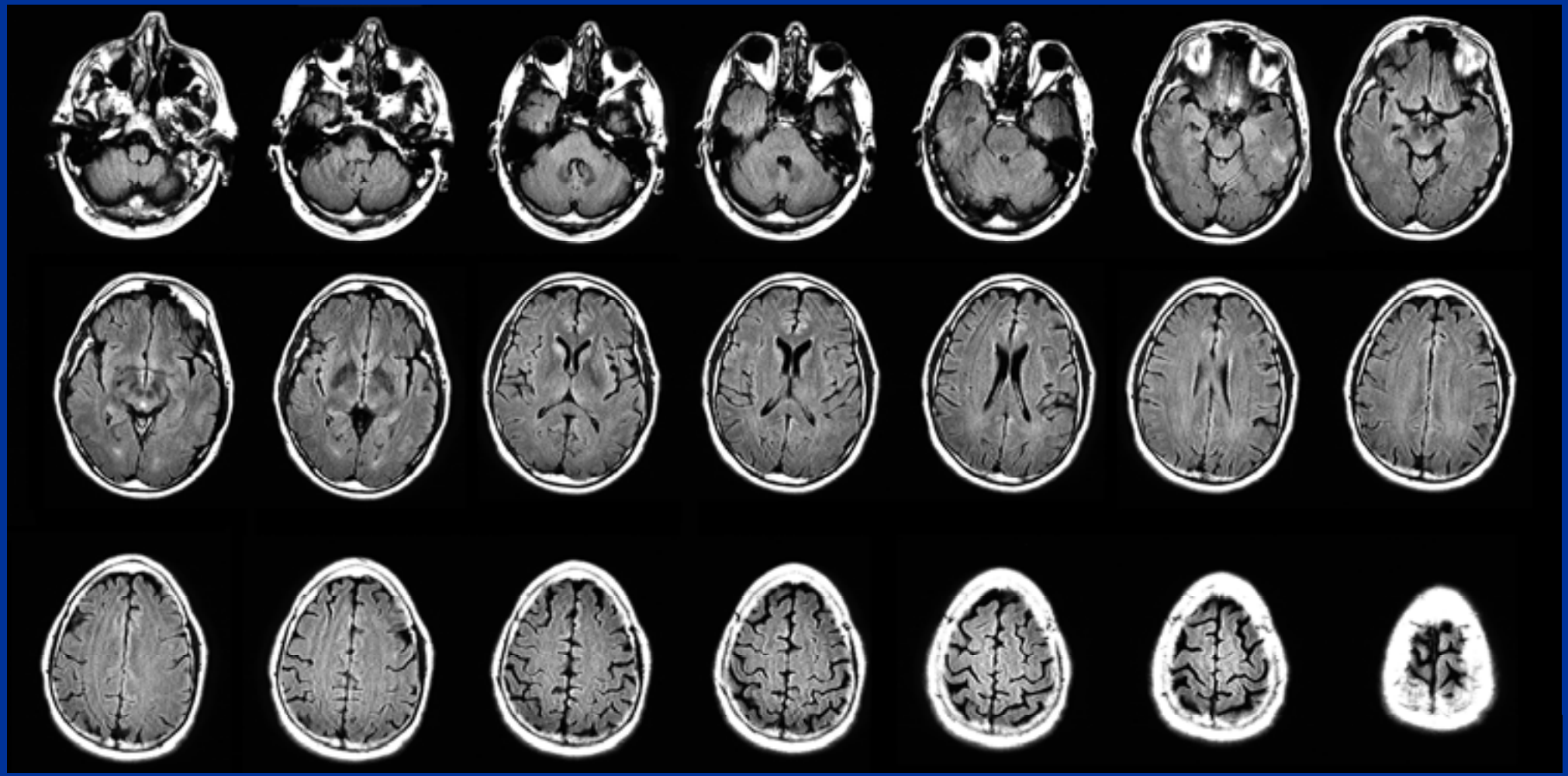
- Increased T2 signal in cortex, deep nuclei
- Increased FLAIR signal in cortex, deep nuclei
- Increased DWI signal in cortex
- No contrast enhancement
- No hemorrhage
- No mass effect
- Usually progressively severe diffuse atrophy

MRI in CJD (T1 sagittal slices)

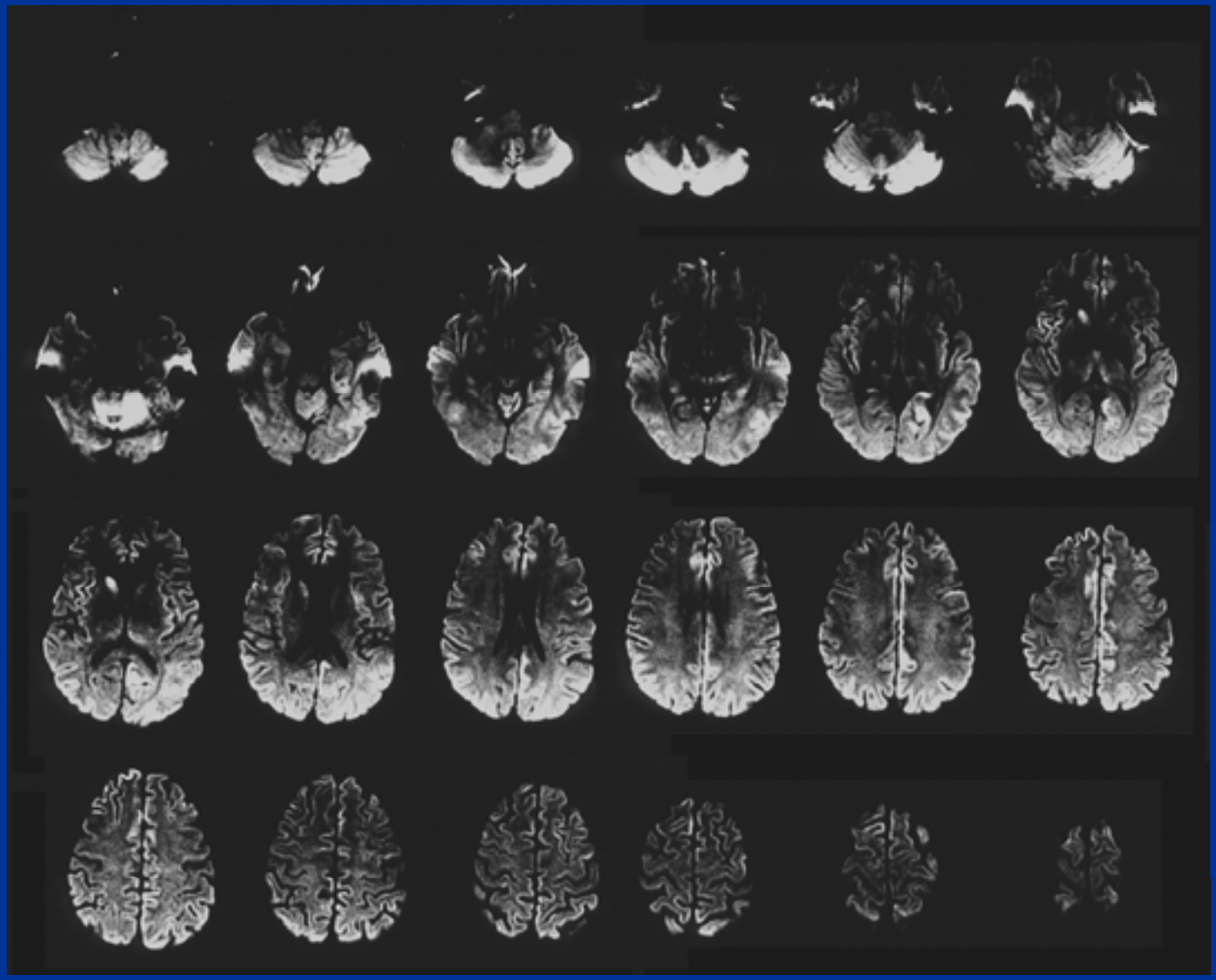




MRI in CJD (FLAIR axial slices)

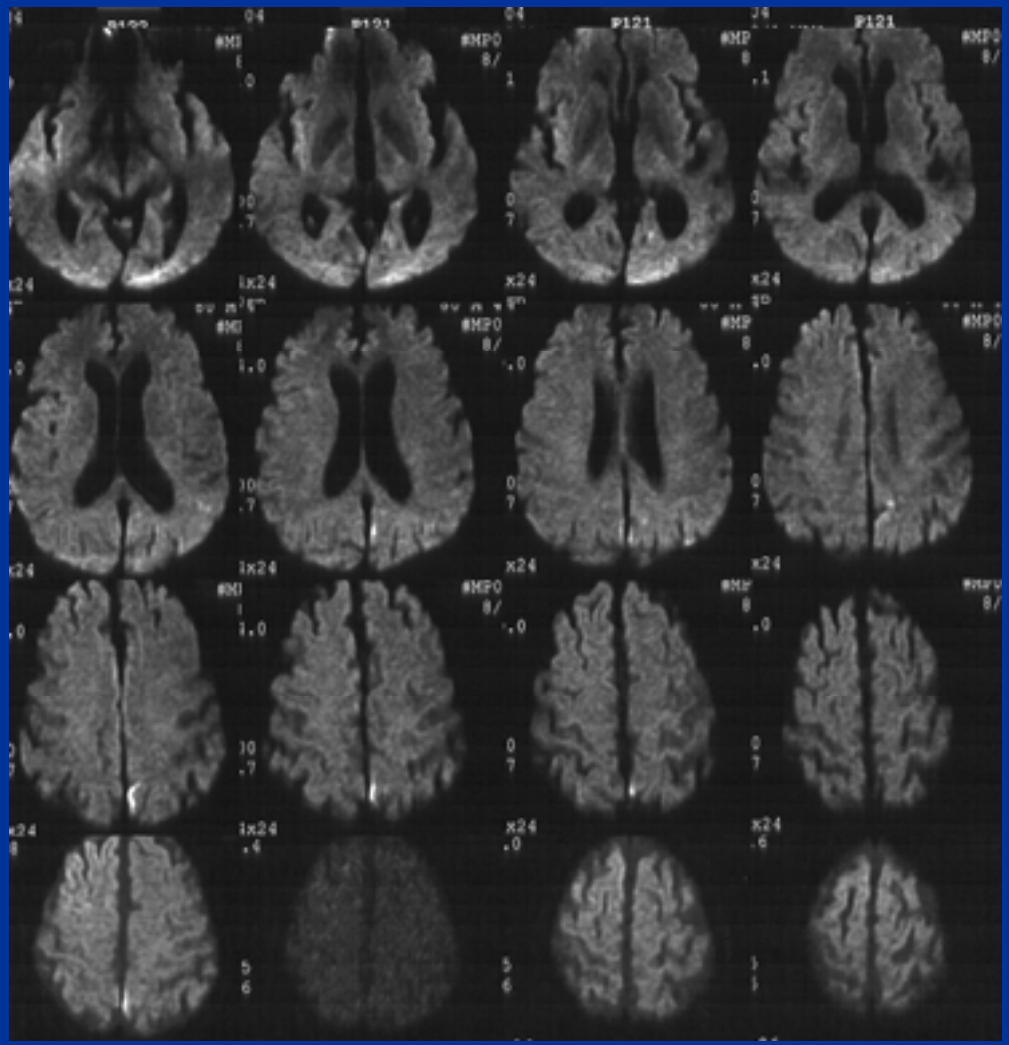


MRI in CJD (DWI axial slices)

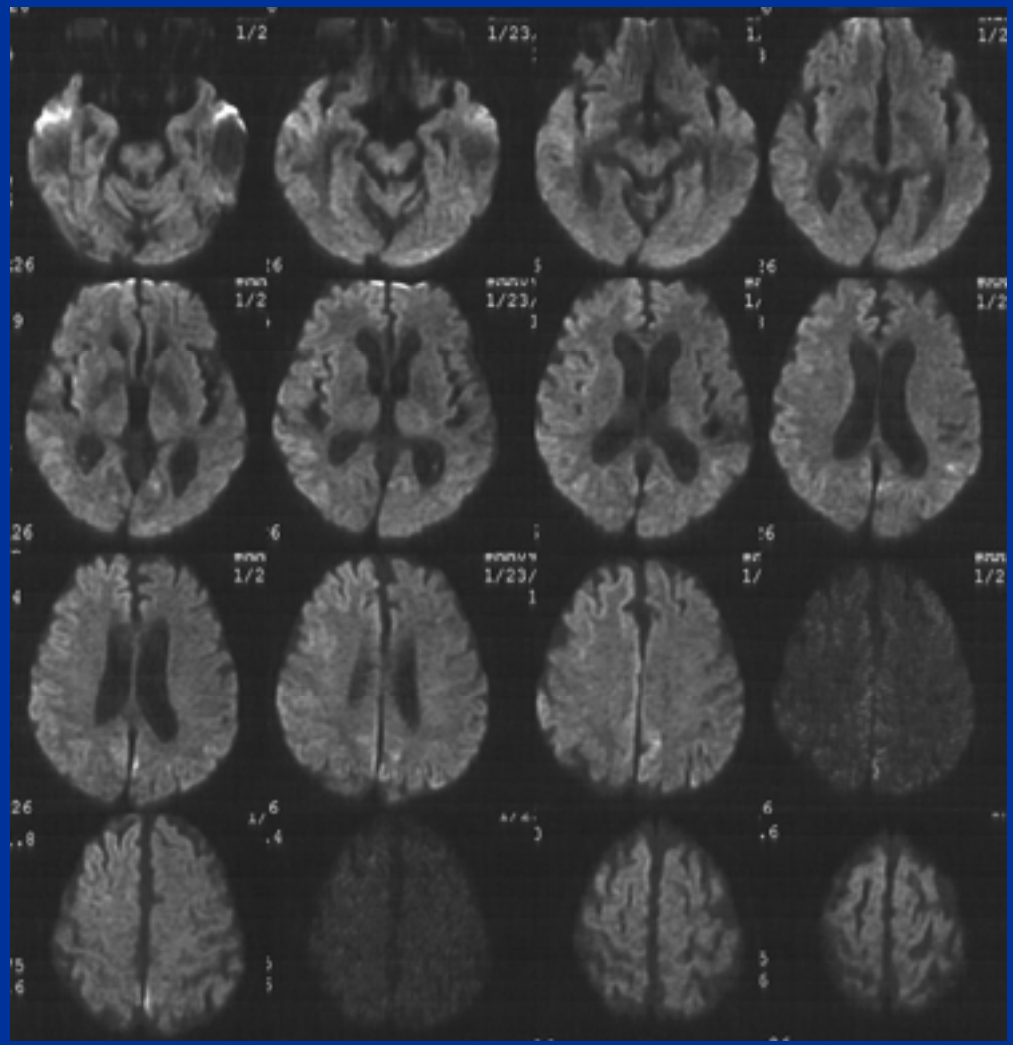


MRI in CJD (DWI changes)

3 months symptoms



7 months symptoms



WHO DIAGNOSTIC CRITERIA: sCJD

- **Probable CJD**
  - Progressive dementia, *and* 2 or 4 clinical features:
    - Myoclonus,
    - Visual or cerebellar impairment
    - Pyramidal or extrapyramidal signs
    - Akinetic mutism
  - Periodic EEG *and/or* 14-3-3(+) and duration < 2 yrs
- **Possible CJD**
  - Same, but duration < 2 yrs and no periodic EEG
- **Definite CJD**
  - Histopathological, Immunohistochemical, WB, EM Dx

Brain Biopsy

- **Pro**
  - may find other more treatable disorder
  - may prove CJD, help prognosis & choice of therapy
- **Con**
  - somewhat invasive
  - requires neurosurgical/pathological precautions
  - may be falsely negative
  - positive test may be construed as “without value”

Brain Biopsy

- **Histopathology**
  - spongiform change (2 – 20 μm vacuoles)
  - neuronal losses
  - astrocytosis
- **Immunohistochemistry**
  - PrP^{RES} presence & type of deposits in brain tissue
- **Western Blot**
  - PrP^{RES} presence and isoform typing

Fatal Insomnia (FFI/sFI)

- isolated persistent severe insomnia
- autonomic nervous system dysfungion
  - dysregulation of blood pressure
  - excessive sweating
  - excessive lacrimation
- ataxia
- dementia (later in course)
- myoclonus, oculomotor impairment

Iatrogenic (non-variant) CJD

Mechanism	Number of cases in world	Incubation period
Human pituitary growth hormone	~ 160	~ 12 yrs
Human dural grafts	~ 160	~ 5 yrs
Human pituitary gonadotrophins	4	~ 13 yrs
Neurosurgical instruments	4	~ 2 yrs
Corneal transplants	3	~ 2 yrs
EEG depth electrodes	2	~ 2 yrs

Kuru

- Described 1957 in Papua New Guinea Fore tribe
- Women and children more affected than men
- Related to handling/consuming human brain tissue
- Incubation period: ~2 – 40 years ?
- Disease course: ~ 9 – 24 months
- Ambulant Stage: tremors, ataxia, postural instability
- Sedentary Stage: myoclonus, chorea, fasciculations, mental slowing, depression
- Terminal Stage: dementia with frontal-release signs, cerebellar dysarthria, akinetic

vCJD

- Typically age < 50 (range 14-74, median 28)
- **Neuropsychiatric/behavioral symptoms first**
- **Painful paresthesias common**
- **Slower progression** (14 mo. median duration)\
- May have myoclonus
- Uncommonly show early weakness, parkinsonism
- NO periodic EEG findings
- NO specific CSF findings (negative 14-3-3)
- **MRI marker** (pulvinar-thalamic high DWI signal)

WHO DIAGNOSTIC CRITERIA: vCJD

I (A) PROGRESSIVE NEUROPSYCHIATRIC DISORDER
(B) DURATION OF ILLNESS > 6 MONTHS
(C) ROUTINE INVESTIGATIONS DON'T SUGGEST ALTERNATE DIAGNOSIS
(D) NO HISTORY OF POTENTIAL IATROGENIC EXPOSURE

II (A) EARLY PSYCHIATRIC SYMPTOMS (depression, anxiety, apathy, withdrawal, delusions)
(B) PERSISTENT PAINFUL SENSORY SYMPTOMS (frank pain +/- unpleasant dysesthesias)
(C) ATAXIA
(D) MYOCLONUS OR CHOREA OR DYSTONIA
(E) DEMENTIA

III (A) EEG ATYPICAL FOR sCJD (gen triphasic periodic complexes ~1Hz) OR NOT DONE
(B) BILATERAL PULVINAR HIGH SIGNAL ON BRAIN MRI

IV (A) POSITIVE TONSIL BIOPSY

DEFINITE: IA (PROGRESSIVE NEUROPSYCHIATRIC DISORDER) and NEUROPATHOLOGICAL CONFIRMATION OF vCJD
(spongiform change & extensive PrP deposits w/florid plaques, through cerebrum & cerebellum)

PROBABLE: I and 4/5 of II and III A and III B or I and IV A