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The CJD Neurological Status Scale: A New Tool for Evaluation of Disease Severity and Progression in Creutzfeldt - Jakob disease

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Abstract

Objectives—To develop a scale sensitive for the neurological manifestations of Creutzfeldt-Jakob disease (CJD).

Methods—A 26-item CJD neurological status scale (CJD-NS) was created based on characteristic disease manifestations. Each sign was assigned to one of eight neurological systems to calculate a total scale score (TSS) and a system involvement score (SIS). The scale was administered to 37 CJD patients, 101 healthy first-degree relatives of the patients and 14 elderly patients with Parkinson's disease (PD).

Results—The mean TSS ($\pm$ SD) was significantly higher in patients with CJD (13.19 ± 5.63) compared to normal controls (0.41 ± 0.78) and PD patients (9.71 ± 3.05). The mean SIS was also significantly different between the CJD (5.19 ± 1.22) and PD (2.78 ± 1.18 **$p < 0.01$**) groups reflecting the disseminated nature of neurological involvement in CJD. Using a cutoff of TSS > 4 yielded a sensitivity of 97% for CJD, and specificity of 100% against healthy controls. All individual items showed excellent specificity against healthy subjects, but sensitivity was highly variable. Repeat assessments of CJD patients over 3-9 months revealed a time-dependent increase of both the TSS and the SIS reflecting the scale's ability to track disease progression.

Conclusions—The CJD-NS scale is sensitive to neurological signs and their progression in CJD patients.

Keywords

Creutzfeldt-Jakob disease; prion; clinical rating scale; progression; disability

Introduction

Creutzfeldt-Jakob disease (CJD) is the most common human prion disease, characterized by rapidly progressive multifocal neurological dysfunction, myoclonic jerks and severe

cognitive impairment [1]. Its pathogenesis involves formation of the abnormal prion protein (PrP^{Sc}) in the central nervous system (CNS) [2]. **Neuronal** degeneration and prion protein deposition are found in the cortex, basal ganglia, thalamus, and cerebellum [3]. It is therefore not surprising that the clinical manifestations of the disease are diverse and include symptoms and signs from many parts of the CNS. The natural history of CJD can be roughly divided into the prodromal stage, the variable neurological stage, and the terminal stage.

CJD can be classified etiologically into familial, sporadic and **transmitted** forms. The familial forms are all caused by mutations in the *PRNP* gene, and the most prevalent mutation **is** found among Libyan Jews [4] **and** is caused by a Glu to Lys substitution at codon 200 (E200K). We have **been studying** this population, which provides a unique opportunity to assess the earliest possible signs and symptoms associated with CJD in a relatively large and **homogenous patient sample**. To correlate these findings with imaging data, it was necessary to develop a method for quantifying neurological findings. Though diagnostic criteria for CJD exist [5,6], they are limited mainly to signs of dementia, ataxia and myoclonus and do not assess well all systems involved, nor do they offer quantification of severity or progression. On the other hand, scales for multi-system neurological diseases such as stroke [7], multiple sclerosis [8], Parkinson's disease (**PD**) [9], and dementia [10] do not cover the extraordinarily wide and unique spectrum of findings characteristic **of** CJD. A standardized method or rating scale for the assessment of CJD is critical, not only to ensure that all relevant functions are examined, but also to provide a quantitative severity measure. Such a quantitative measure of disease severity is essential to ensure comparability of samples across studies, to evaluate medication effects and allow for correlations with imaging and neuropathological findings.

We have therefore devised a new scale aimed at assessing the spectrum of neurological systems affected by CJD with emphasis on those **signs** that are typical for the disease. In this report, we present our proposed scale, the CJD Neurological Status (CJD-NS) scale. To evaluate its utility we administered it prospectively to 138 subjects in the context of a large clinical-imaging study of familial CJD and to 14 patients with Parkinson's disease. We here describe its ability to evaluate disease severity and progression.

Methods

Subjects

The study population consisted of 1. CJD patients, both familial (fCJD) and sporadic (sCJD). 2. **First-degree** relatives of the patients who either **carried** the E200K mutation (referred to as C+) or **did** not carry the mutation (C-).

The CJD patients and their healthy relatives were all participants in a prospective longitudinal study [11]. Patients fulfilled WHO criteria for probable CJD [6] and were followed until death to confirm the diagnosis. Healthy subjects, both positive and negative for the E200K mutation, were recruited from the same families and were normal by history, neurological and neuropsychological examinations. Elderly individuals **suffering from** PD, **some with** concomitant illnesses (**e.g. stroke, dementia**) were evaluated as part of their routine care at our movement disorders clinic. These patients **had** multiple neurological systems involved and may potentially be confused with CJD. The diagnosis of PD was based on the UK Brain Bank criteria [12]. After initial evaluation of the first version of the scale in seven CJD patients, the final version was tested on a total of 152 subjects consisting of 37 CJD patients (32 familial and 5 sporadic), 50 first degree relatives carrying the E200K mutation (C+), and 51 first degree relatives not carrying the E200K mutation (C-) and 14 elderly PD patients. All findings reported here (other than the progression analysis) pertain to the first study visit where data were available. All subjects underwent a detailed

neurological examination, the Mini-Mental Status examination (MMS) [10], and the Frontal Assessment Battery (FAB) [13], by neurologists blind to genotype. Healthy subjects were followed annually while 14 of the patients with CJD had repeated assessments over a 3-5 month period.

The CJD-NS scale

The scale consists of **twenty-six** items; each representing a neurological sign that is frequently observed during the course of fCJD [14]. Since we assumed a finer gradation would not achieve high reliability. The signs were rated as 0= absent (if the abnormal sign was not evoked), 1=mild (if the abnormal sign was mild or equivocal) and 2=obvious/severe (when the sign was severe or definite).

The 26 items of the CJD clinical neurological scale (CJD-CNS) (Figure 1) were assigned into eight neurological systems. Since certain signs can be attributed to more than one neurological system, we categorized them according to the system the involvement of which is the most likely cause of this sign in CJD.

The scale items were as follows:

Disturbances in neuronal circuits associated with vision and ocular motility: visual field defect, defect in pursuit or saccades, optic ataxia.

Brain stem dysfunction: Dysarthria, dysphonia and nystagmus.

Cerebellar dysfunction: Tremor, trunk or gait ataxia, limb ataxia.

Extrapyramidal signs: Bradykinesia, rigidity, dystonia and staring gaze.

Pyramidal signs: Weakness, impaired dexterity, spasticity, hyper-reflexia, extensor plantar responses.

Frontal and other cortical release signs: Glabellar, snout, palmomental, grasp.

Neuropathy: Hyporeflexia or areflexia.

Measures of cortical dysfunction/hyperexcitability: Impaired consciousness, seizures, and myoclonus.

For longitudinal analysis, **since** certain signs may be difficult to assess objectively in patients with advanced disease, a sign that was previously evoked but could not be re-tested due to the **condition** of the patient (e.g. visual **field** defect in a comatose patient) was carried forward in **subsequent** observations.

Two measures were derived from the scale: 1 .The total scale score (TSS) which is the sum of the scores of the 26 individual items (**maximum 52**). 2. The system involvement score (SIS) which is the sum of the affected systems in a certain individual. For each of the eight systems, a score of **1** indicated involvement of **this** system. The SIS therefore ranged from 0 (apparently healthy individual) to 8 (all neural systems affected).

Evaluation of disease progression

As disease progressed, greater severity would manifest itself by addition of new signs as well as spread of signs within the same system and into other neurological systems. Progression was therefore assessed by measuring the TSS and SIS in those patients (N=14) **who were subjected to** two or more examinations.

Statistical analysis

Sensitivity and specificity were computed by standard formulas combining “mild” and “severe” into “present”, and testing them against “absent”. Differences in distributions were assessed by contingency analysis and the χ^2 test, with the significance determined by the likelihood ratio method. Continuous variables were evaluated by linear regressions and the product-moment correlation coefficients, as well as appropriate Analysis of Variance (ANOVA) or Analysis of Covariance (ANCOVA) designs. Significance threshold was set at $\alpha=.05$.

Results

1. Initial reliability testing

A preliminary version of the scale was tested independently by two physicians (LE and JC) on seven patients and then verified by a joint examination. Most measures showed 100% concordance. Some discordance was evident for staring gaze, visual field defect, nystagmus, limb ataxia, and bradykinesia (one case each) and for the glabellar sign (two patients). This resulted in modification of the scale into 26 items that were considered readily definable signs which are frequently observed during the course of CJD (Figure 1). This version was tested on the final samples of 152 subjects described in Table 1.

2. Comparison of groups

In order to assess whether the scale has discriminatory power we compared the scale scores between patients with CJD, healthy controls and patients with PD.

2a. CJD and healthy individuals—Since there were no significant differences between the patients carrying the E200K (fCJD) mutation and patients who did not carry the mutation (sCJD) in either the TSS or the distribution of any item, they were combined into a total sample of 37 CJD patients (mean age $\pm$ SD 62 $\pm$ 8 years, 54% male). Similarly, there was no significant difference between the apparently healthy subjects carrying (C+) and not carrying (C−) the E200K mutation in their mean total score (0.45 $\pm$.89 vs. 0.41 $\pm$.78). However, both mean and variance were slightly higher in the mutation-positive subjects, and there is always the possibility that some of them are in the process of converting into the initial disease phase. Therefore, for most quantitative analyses, we used only the mutation-negative subjects as healthy controls.

The mean TSS $\pm$ SD was significantly higher ($p < 0.01$) in patients with CJD (13.19 $\pm$ 5.63) compared to the healthy subjects (C+ and C−) (0.41 $\pm$ 0.78). All but one CJD patient (who was examined one month after the first sign of the disease) had a TSS greater than 4 suggesting that this score could be used as a cutoff between patients with CJD and healthy subjects (C+ and C−). The mean SIS for CJD patients was 5.19 $\pm$ 1.22 (range 3-7) reflecting the disseminated nature of the disease that affected multiple brain areas and neurological systems.

2b. Comparison with PD—The mean TSS $\pm$ SD was significantly higher ($p < 0.01$) in patients with CJD (13.19 $\pm$ 5.63) compared to the patients with PD (9.71 $\pm$ 3.05). The mean SIS was also significantly different between the two groups (5.19 $\pm$ 1.22 in the CJD group vs. 2.78 $\pm$ 1.18 in the PD group, $p < 0.01$). When distribution was tested it was found that 95% of CJD patients had an involvement of 4 systems or more while 78% of PD patients had SIS $\leq$ 4 indicating that the SIS parameter has the best the discriminative value between CJD and PD.

2c. Sensitivity and specificity of the scale scores—We conducted an ANCOVA on TSS with diagnosis (CJD, PD, **and** C−) and gender as between-groups factors and age as a covariate. Gender **and** age did not yield significant effects or interactions. With a simple ANOVA by diagnosis, diagnosis effect was highly significant ($p<.0001$), **and** all three diagnoses were significantly different by post-hoc *t* tests. All but one CJD patient had a TSS score greater than 4 and all but one **clinically unaffected carrier** had a score lower than 4. There was substantial overlap, however, between CJD and PD patients. Using a cutoff of total TSS > 4 yielded a sensitivity of 97% for CJD, and specificities of 100% against healthy controls (**C+ and C−**) and 0 against PD.

3. Item analysis

In order to examine whether the signs chosen for the scale are indeed characteristic for CJD, contingency analysis was also conducted to compare the distribution of each item between the CJD patients and the healthy, non-carrier controls (C−, $n=51$). These results are detailed in Table 2. While all items showed excellent specificity against **healthy non carrier individuals (C−)**, and all significantly discriminated the samples, sensitivity was highly variable.

4. Assessment of disease progression

In order to assess disease progression we measured the change in TSS and SIS in the 14 patients who had repeated examinations. The results are presented in Figure 2A in a cross sectional manner **for all observations where** the **time axis** denotes the **interval between examinations** and not disease onset. As can be seen, most patients progressed in their TSS with a mean $\pm$ SD increase of 3.8 ± 3.2 points per month of follow up.

Seven patients had three examinations and their mean TSS $\pm$ SD values were 8.7 ± 2.14 , 10.0 ± 4.0 and 19.0 ± 9.4 for visits 1, 2 and 3, respectively. In a simple analysis of variance of the total scale score by visit, there was a significant effect of visit $F_{2, 18}=6.08$, $p<.01$). The time course of TSS change relative to duration of disease is presented in Figure 2B for the 7 patients with 3 evaluations as well as the other seven patients who had 2 evaluations. As can be seen, all but two subjects progressed in TSS but the rate was clearly different in individual patients.

Disease progression was also evident by the SIS score (Figure 3) reflecting the spread of the disease with time and the dissemination of the disease to additional neurological systems.

Discussion

To our knowledge, this is the first attempt to quantify and categorize neurological findings in CJD. The TSS of the CJD-NS **offers** excellent discrimination against healthy subjects and PD patients as well as **sensitive** evaluation of the disease burden in CJD patients. The SIS reflects the disseminated nature of CJD throughout the central nervous system and had **a good** discriminative value against elderly patients with PD. In addition, the scale reflects disease progression in repeated assessments of CJD patients over 3-5 months, which revealed a time-dependent increase of both the CJD-NS scores TSS and SIS. This rating scale has been used successfully in our study of familial CJD, and has **provided** informative relationships with imaging findings [11,15].

Desirable as it would be to offer diagnostic utility in the earliest prodromal stage of CJD, our scale was not intended for this purpose. This stage is characterized by nonspecific neuropsychiatric symptoms [16,17], depression [18], fatigue, sleep and autonomic dysfunctions [19], and behavioral disturbances [20,21]. Mental disturbances, including

aggressive behavior, psychosis and depression [14], as well as other non specific prodromal symptoms including headache, loss of appetite and loss of weight **have** also **been** reported in patients with familial CJD carrying the E200K mutation [22]. Accurate diagnosis at this stage must therefore await the development of laboratory markers and it is possible that MRI may be helpful in this regard [15].

In contrast to the relatively stereotyped phenomenology of variant CJD, which has a known progression from behavioral changes to involuntary movements and dementia, [23] and Gerstmann-Sträussler-Scheinker disease [24] in which cerebellar signs predominate over many years, sporadic CJD [19,21] and familial CJD associated with the E200K mutation [22,25] are heterogeneous in both presentation and progression. There are well known phenotypic variants of CJD including the Heidenhain variant [26], which presents with visual disturbances and the Oppenheimer-Brownell variant [27], which presents with ataxia. In contrast to the variability and non-specific nature of the prodromal symptoms, the neurological signs, once developed, may be quite typical and include cognitive dysfunction, myoclonic jerks and ataxia [22,24]. We therefore chose to base the CJD-NS scale on signs and not on the initial symptoms. This is probably the earliest point at which a reliable diagnosis can be suspected on purely clinical grounds, and it would be useful to have a unified structured tool for the examination.

The main intended use of this scale is to characterize CJD patients and quantify their disease severity, **for** ensuring comparability between studies and across patients and it seems that the TSS and SIS well reflect the burden of the disease. **Though** we present diagnostic discriminative data, we do not suggest that this scale by itself can be useful for the diagnosis of CJD. On the other hand, our scale does appear useful for tracking the progression of the disease. The TSS reflects the addition of new signs as well as the **accumulated** severity of existing signs. The SIS reflects the dissemination of the disease to various structures of the CNS and the involvement of new systems as the disease progresses. Figure 2 demonstrates a variable rate of progression in individual patients. This observation strengthens the need for a standardized severity scale, since duration of disease does not predict severity very well. Furthermore, our current limited longitudinal data suggest that the progression of disease severity is nonlinear. Thus, prediction of deterioration may be complex, and it will be important to collect more quantitative data on the natural history and rate of progression with standardized methods, such as the CJD-NS.

The proposed scale is based on our clinical experience with CJD patients and literature review. Its validation in the current samples is encouraging although it was drawn from a small population sharing major genetic, cultural and environmental background. The fact that the patients were examined fairly early in the course of the disease, demonstrates the value of the proposed scale. Our scale was applied mainly to a population of patients with familial CJD and whether the CJD-NS developed for this form of CJD will be applicable to the sporadic disorder remains to be confirmed by future studies in a larger number of patients with the sporadic disorder. However, since there is strong evidence that the E200K form is very similar to the sporadic disease clinically [22], neuropathologically [28] and radiologically [11] we believe there is a good chance that the results would be applicable for sCJD. Development of such a score **may** also **be useful** to monitor the effect of therapy on rate of disease progression.

The proposed CJD-NS scale **is limited** since it does not reflect the cognitive status, which is an essential component of CJD phenomenology; therefore, an independent assessment of cognitive performance needs to be performed. We have used the simple and rapid MMS [10] as adjunct to the CNS-NS, and the initial results are encouraging, but larger studies, both cross-sectional and longitudinal, are necessary.

In Conclusion

The proposed CJD-NS scale is valuable for assessing disease severity and progression in CJD patients and may be useful **both** as a clinical and **a** research tool, **potentially** monitoring the effect of **genetic, environmental and therapeutic factors** on disease progression.

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Neurological condition	Notes	Assessment and treatment
	<ul style="list-style-type: none">• APACHE II• APACHE II	
Neurological disorders, stroke, aneurysm, TIA, epilepsy and multiple sclerosis		
• Stroke (acute stroke)		
• TIA (transient ischaemic attack)		
• Epilepsy		
• Multiple sclerosis		
• Parkinson's disease		
• Alzheimer's disease		
• Huntington's disease		
• Amyotrophic lateral sclerosis (ALS)		
• Spina		
• Head injury		
• Concussion		
• Skull fracture		
• Brain tumour		
• Meningitis		
• Encephalitis		
• Hydrocephalus		
• Epilepsy		
• Multiple sclerosis		
• Parkinson's disease		
• Alzheimer's disease		
• Huntington's disease		
• Amyotrophic lateral sclerosis (ALS)		
• Spina		
• Head injury		
• Concussion		
• Skull fracture		
• Brain tumour		
• Meningitis		
• Encephalitis		
• Hydrocephalus		
• Epilepsy		
• Multiple sclerosis		
• Parkinson's disease		
• Alzheimer's disease		
• Huntington's disease		
• Amyotrophic lateral sclerosis (ALS)		
• Spina		
• Head injury		
• Concussion		
• Skull fracture		
• Brain tumour		
• Meningitis		
• Encephalitis		
• Hydrocephalus		
• Epilepsy		

Figure 1.
CJD-NS: The Creutzfeldt-Jakob disease Neurological scale.

Figure 2. Progression of CNS-NS Total Severity Score (TSS) relative to elapsed time between evaluations

Progression of CNS-NS Total Severity Score (TSS) relative to time. Time is presented in months and TSS was calculated as described in the methods. (2A): TSS is presented for 14 patients with at least 2 examinations. Each point represents the change between first and last examination in each patient. (2B): The change in TSS relative to disease duration for 7 patients with 3 consecutive examinations and 7 additional patients with 2 consecutive examinations.

Figure 3. Progression of CJD-NS System Involvement Scores

Progression of CJD-NS System Involvement Scores (SIS) relative to disease duration in seven patients who had three or more evaluations. Each line represents the scores in one patient.

Table 1

Subjects' characteristics

Sample	Number	Mean age $\pm$ SD (years)	Gender (% males)
P+	32	61 $\pm$ 8	19 (59%)
P-	5	66 $\pm$ 5	1 (20%)
C+	50	49 $\pm$ 13	33 (66%)
C-	51	50 $\pm$ 10	19 (37%)
PD	14	71 $\pm$ 14	11(79%)

C+: Apparently healthy first-degree relatives of CJD patients carrying the E200K mutation, C-: Apparently healthy first-degree relatives of CJD patients not carrying the E200K mutation. P+: CJD patients carrying the E200K mutation, P-: CJD patients not carrying the E200K mutation. PD: Parkinson's disease patients

Table 2

Sensitivity and specificity of the various scale items: comparison of CJD patients and controls (healthy first degree relatives of patients with CJD)

Item	Sensitivity [%]	Specificity [%]	P
Limb Ataxia	76	100	<.0001
Trunkal Ataxia	68	98	<.0001
Snout	63	84	<.0001
Staring Gaze	58	100	<.0001
Rigidity	55	94	<.0001
Babinski	55	98	<.0001
Dysarthria	47	100	<.0001
Glabellar	47	96	<.0001
Palmomental	45	98	<.0001
Myoclonus	42	100	<.0001
Dysphonia	34	100	<.0001
Dexterity	34	100	<.0001
Pursuit	32	100	<.0001
Spasticity	32	100	<.001
Tremor	29	98	.0001
Dystonia	29	100	<.0001
Weakness	29	98	<.0001
Bradykinesia	24	96	<.005
Hyperreflexia	24	100	<.0001
Nystagmus	16	100	.001
Optic Ataxia	16	100	.001
Grasp	16	100	.001
Hyporreflexia	16	100	.001
Impaired Consciousness	11	100	<.01
Visual Field Defect	8	100	<.05
Seizures	8	100	<.05
Sensory Loss	5	98	NS

Sensitivity and specificity of the various scale items: comparison of CJD patients (n=37) and controls (C= n=51).significance levels refer to the χ^2 test with the significance determined by the likelihood ratio method.