Movement Disorders
Vol. 24, No. 4, 2009, pp. 509–518
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A Novel Global Assessment Scale for Wilson's Disease (GAS for WD)

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Video 

Abstract: Wilson's disease (WD) is an inherited disorder of copper metabolism. Despite being treatable, patients with WD suffer severe disabilities due to delay in initiation and difficulty in monitoring treatment. We propose a two tier, ***Global Assessment Scale for Wilson's Disease*** (GAS for WD) that grades the multisystemic manifestations of the disease. **Tier 1** scores the global disability in four domains: Liver, Cognition and behavior, Motor, and Osseomuscular. **Tier 2** is multidimensional scale for a fine grained evaluation of the neurological dysfunction. We prospectively validated this scale in 30 patients with WD. Both tiers had a high inter-rater reliability (Intraclass correlation coefficient ICC (A, 2) = 0.96–1.0). Tier 2 items were internally consistent (Cronbach's α = 0.89) and factorial analysis showed that 90.3% of the Tier 2 total score variance was determined by seven factors. Scores of both tiers were commensurate with the disease burden as assessed by standard disability scales (Child Pugh, UPDRS, SS3, and CGI) and satisfied criteria for validity. Longitudinal follow-up over 1.5 years showed that the scale was sensitive to clinical change. This suggests that GAS for WD is a practical tool with potential applications in management of patients, and in testing and comparison of treatment regimens. © 2008 Movement Disorder Society

Key words: Wilson's disease; disability scale; reliability; responsiveness; validation

Wilson's Disease (WD) (MIM #277900) is a rare autosomal recessive disorder of copper metabolism.[1] It usually manifests within the first three decades with liver dysfunction, extrapyramidal, neuropsychiatric, or osseomuscular (i.e., skeletal or musculoskeletal) symptoms, and has marked inter- and intrafamilial clinical heterogeneity.[1–4] Untreated, WD is fatal.[5]

Both symptomatic and asymptomatic patients with WD require lifelong decoppering with close clinical monitoring.[1] Objective and quantitative measure of disease burden is also essential to test and compare various treatment regimens. However, it is difficult to discern and record small changes in disability based solely upon patient and caregiver accounts, and routine clinical assessments, especially since WD affects multiple systems, with variable disease evolution and treatment response in each system.[1,6] In clinical practice, proxy scales or scales grading limited aspects of WD are used to assess disease burden.[7–14] Recently, a multisystemic WD scale has been proposed by Leinweber et al., although its responsiveness has not been reported.[15]

We propose a novel Global Assessment Scale for Wilson's Disease (GAS for WD) to capture its multisystemic manifestations and track disease progression

Additional supporting information may be found in the online version of this article.

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Potential conflict of interest: None reported.

Received 21 February 2008; Revised 17 June 2008; Accepted 21 June 2008

Published online 29 December 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22231

TABLE 1. *Global Assessment Scale for Wilson's Disease (GAS for WD)*

Instructions

Grades based on historical accounts, such as Tier 1 (Cognition and behaviour domain) and Tier 2 (Item 2: Scholastic performance; Item 3: Depression; Item 4: Psychosis) should reflect patient's clinical status over the previous one month. All other grades should reflect patient's clinical status at the time of administering the scale.

Rate only "what you see". Grade each domain and item independently based upon the scale anchors, for instance, in a patient with incapacitating dystonia and tremor, grade both Tier 2 Item 5 (Dystonia) and Item 6 (Tremor), as 4.

If a particular domain or item cannot be evaluated assign zero score appended by an asterisk (0*). For example, Tier 1 Osseomuscular domain is graded as 0* if there is no clinical evidence of osseomuscular involvement and X-rays are not available; similarly, Tier 2 Item 13 (KF rings) is graded as 0*, if KF rings are not visible with naked eye and a slit lamp examination cannot be done.

If in doubt between two scores assign the higher score.

Activities of Daily Living (ADL) refers to dressing, personal hygiene, eating, walking or any other day to day activity.

Tier 1: Global Disability

1. L - Liver[a]

- **L 0:** No past or ongoing / active liver disease
- **L 1:** Liver disease in past but no ongoing / active liver disease
- **L 2:** Ongoing / active liver disease but no evidence for cirrhosis[b]
- **L 3:** Compensated cirrhosis
- **L 4:** Decompensated[c] cirrhosis
- **L 5:** Potentially life threatening liver disease[d]

[a]Clinical, biochemical and abdominal ultrasound evidence for liver disease; liver biopsy is optional.
[b]Clinical or ultrasound evidence of cirrhosis or history of complications of cirrhosis; liver biopsy is optional.
[c]Hepatic encephalopathy, porto-systemic bleeding, ascites.
[d]Acute liver failure, liver disease with massive hemolysis or any liver disease requiring liver transplant.

2. C - Cognition and behavior[e]

- **C 0:** Normal
- **C 1:** Symptoms noticed by parents, caregivers, immediate family members, or at school or work. Patient functions normally.
- **C 2:** Obvious problems at home, school and work but can function at normal level with extra effort or help
- **C 3:** Serious problems at home, school and work. Unable to function at normal level, e.g., impaired interpersonal relationships, dropping grades at school or work
- **C 4**: Unable to function independently except for simple ADL, *e.g*., severely impaired interpersonal relations, discontinued school or work; and needs considerable help, antidepressants or antipsychotics
- **C 5:** Dependent on caregivers even for simple ADL; institutionalized or needs to be restrained at home and is on antipsychotics or antidepressants

[e]Related to intellectual decline, depression, psychosis.

3. M - Motor[f]

- **M 0:** Asymptomatic or normal
- **M 1:** Subtle clinical signs
- **M 2:** Difficulty in ADL but independent
- **M 3:** Requires help in ADL
- **M 4:** Dependent on others for ADL
- **M 5:** Bed bound

[f]Neurological motor impairment.

4. O - Osseomuscular[g]

- **O 0:** Normal
- **O 1:** Abnormal skeletal X-ray; asymptomatic
- **O 2:** Difficulty in ADL but independent
- **O 3:** Requires help in ADL
- **O 4:** Dependent on others for ADL
- **O 5:** Fracture or bedbound

[g]Bone, spinal or joint pain, swelling or deformity, or proximal muscle weakness.

Tier 2: Neurological Assessment

1. Wilson's facies

- **0**. Normal
- **1**. Open mouth or facetious smile
- **2**. Open mouth and facetious smile may have excessive salivation
- **3**. Early dull look[h]
- **4**. Dull look[h]

[h]Psuedoptosis, decreased eye contact, decreased exploratory eye movements, drooping angle of mouth, delayed or no change in facial expressions.

TABLE 1. *(Continued)*

2. Scholastic Performance
- **0**. No intellectual decline[i]; no change in academic or work performance
- **1**. Mild intellectual decline[i]; with help maintains grades or performance at work
- **2**. Intellectual decline[i]; clear deterioration in academic or work performance with dropping grades
- **3**. Fails school and unable to continue schooling or work
- **4**. Requires help in day to day intellectual activities[i]

[i]Forgetfulness, difficulty in playing with friends, doing simple chores at home, running errands or difficulty in ADL (not explained by physical disability).

3. Depression[j]
- **0**. Absent
- **1**. Subtle symptoms only recognized by parents, caregivers, immediate family members, or at school or work; not normal but does not interfere with family life, school or work
- **2**. Mildly interferes with family life, school or work
- **3**. Severely disrupts with family life, school or work; requires antidepressants
- **4**. Attempts suicide; requires hospitalization

[j]Sadness of mood or disinterest in almost all or all activities with or without somatic symptoms (unexplained weight loss, alteration in sleep pattern, fatigue, loss of energy, feeling of worthlessness, inappropriate guilt, decreased concentration, indecisiveness).

4. Psychosis[k]
- **0**. Absent
- **1**. Subtle symptoms; not normal but does not interfere with family life, school or work
- **2**. Mildly interferes with family life, school or work
- **3**. Severely disrupts family life, social life or relations and performance at school or work; requires antipsychotics
- **4**. Attempted suicide or murder; requires restraining or hospitalization

[k]Elevated mood, irritability, agitation, aggressiveness (e.g. throws temper tantrums, verbally or physically abusive or violent), flight of ideas, pressure of speech, motor restlessness (fidgety, hyperactive, runs away from home), impulsive behaviour, hypersexuality, disinhibition, alcohol or drug abuse or addictions, delusions, hallucinations, threat or attempt of suicide or murder.

5. Dystonia
- **0**. Absent
- **1**. Dystonia that does not restrict any activity
- **2**. Restricts ADL but independent
- **3**. Restricts ADL; needs help
- **4**. Bedbound

6. Tremor (rest, postural or action)
- **0**. Absent
- **1**. Tremor that does not restrict any activity
- **2**. Restricts ADL but independent
- **3**. Restricts ADL; needs help
- **4**. Bedbound

7. Chorea
- **0**. Absent
- **1**. Chorea that does not restrict any activity
- **2**. Restricts ADL but independent
- **3**. Restricts ADL; needs help
- **4**. Bedbound

8. Parkinsonism
- **0**. Absent
- **1**. Parkinsonism that does not restrict any activity
- **2**. Restricts ADL but independent
- **3**. Restricts ADL; needs help
- **4**. Bedbound

9. Speech
- **0**. Normal
- **1**. Slurred but easily intelligible
- **2**. Slurred; intelligible with difficulty
- **3**. Unintelligible
- **4**. Mute or Anarthric

10. Swallowing
- **0**. Normal
- **1**. Chokes occasionally
- **2**. Chokes frequently
- **3**. Chokes with each meal
- **4**. Aspiration pneumonia or on feeding tube

TABLE 1. *(Continued)*

11. Salivation
- **0**. Normal
- **1**. Wets pillow at night; normal during day
- **2**. Wet lips and angle of mouth; mouth filled with saliva; requires frequent wiping;
- **3**. Intermittent drooling
- **4**. Constant troublesome drooling

12. Posture and Gait (not due to solely osseomuscular involvement)
- **0**. Normal erect posture and gait
- **1**. Abnormal posture but stands and walks independently.
- **2**. Posture clearly abnormal; stands and walks with support of a walking stick or one person.
- **3**. Cannot stand and walk without considerable help and can fall easily if unsupported.
- **4**. Bedbound

13. Kayser Fleischer rings
- **0**. Absent
- **1**. Visualized with slit lamp
- **2**. Incomplete ring (restricted to superior, inferior or both corneal poles) visible with naked eye using torch
- **3**. Complete thin ring visible with naked eye using torch
- **4**. Complete thick ring visible with naked eye using torch

14. Uncommon

Records the presence (1) or absence (0) of each of the following features:
- emotional lability
- seizures over preceding 1 month
- myoclonus
- stereotypy
- tics
- pyramidal signs
- eye movement abnormalities

Count the number of the above features that are present (upto a maximum of 4)

and treatment response. In this article, we present the results of a prospective pilot study in which we administered the scale to 30 patients with WD and followed them up longitudinally.

METHODS

GAS for WD is a two Tier scale (Table 1) developed based on literature review and consultation with specialists and caregivers (supplementary data).[1–6,16–20] It is administered on each patient visit once WD is diagnosed.

Tier 1: Global Disability covers 4 domains: Liver, Cognition and behavior, Motor, and Osseomuscular. The Cognition and behavior, and Motor domains measure two different aspects of WD-related neurological dysfunction. Each domain is scored independently on an ascending six point scale (0–5) generating four integers, each prefixed with its domain identifier (L, C, M, and O, respectively). Since the four domains reflect noncommensurable facets of WD, their scores are not summed.

Tier 2: Neurological Assessment assesses different aspects of neurological dysfunction due to WD in detail under 14 items: Wilson's facies (*Item 1*), cognition and behavior (*Items 2–4*), movement disorders (*Items 5–8*), bulbar symptoms (*Items 9–11*), posture and gait impairment (*Item 12*), Kayser Fleischer (KF) rings (*Item 13*), and uncommon (*Item 14*). Each item is scored on an ascending five point scale, (0–4) and the scores are summed to obtain the Tier 2 total score (0–56).

Patient Population

A validation study for GAS for WD was conducted at Jaslok Hospital and Research Center, Mumbai, India after approval by the Institutional Review Board. All patients with WD seen from April 2006 to June 2007 were prospectively recruited. WD was diagnosed based on a combination of characteristic clinical features, KF rings, low serum ceruloplasmin, high urinary copper, high liver copper, and brain MRI.[16] Depending on the presence or absence of symptoms, patients with WD were classified as symptomatic and presymptomatic, respectively. The latter were identified during screening of family members of index cases.

Patients were independently rated by two neurologists (MB, AA) on GAS for WD, Child Pugh scale for cirrhosis[21]; Unified Parkinson's Disease Rating Scale (UPDRS) parts I (mental dysfunction) and III (motor examination)[22]; and two global disability scales, the three-point Severity Scale (SS3),[23] and Clinician Global Impression (CGI) items 1 (severity of illness) and 2 (global improvement).[24] The patients were then

TABLE 2. *Spearman's rank correlation coefficients for the 4 Tier 1 domains and the Tier 2 total score (n = 30)*

		Tier 1 domains			
		Cognition & behavior	Motor	Osseomuscular	Tier 2 total score
Tier 1 domains	Liver	0.06	0.00	0.17	0.14
	Cognition & behavior	1.00	0.49**	0.43***	0.91*
	Motor		1.00	0.26	0.65*
	Osseomuscular			1.00	0.50**

*$P < 0.001$
**$P = 0.001$–0.01
***$P = 0.01$–0.02.

assessed longitudinally at intervals of roughly 3 months till October 2007.

Validation and Statistical Analysis

Reliability of a scale refers to its reproducibility (inter and intra-rater), and the internal consistency of a multidimensional scale. Tier 1 and 2 scores at first assessment were used to compute the inter-rater reliability using intraclass correlation coefficient for agreement (ICC (A, 2)).[25] Cronbach's α was used as a measure of the internal consistency of Tier 2, and the contribution of the individual items to the total Tier 2 score variance was assessed using factor analysis.[26]

Validity of a scale refers to evidence that a scale is measuring what is intended. Since there is no gold standard for assessing WD-related disability, evaluation of its validity relies on indirect measures. **Criterion validity** for Tier 1 and Tier 2 was assessed by comparing their scores with SS3 and CGI item 1. **Convergent validity** was established by assessing the degree to which GAS for WD subscores correlated with related disability scales (Child Pugh; UPDRS parts I and III). Spearman rank correlation coefficients were used for score correlations and interpreted empirically as weak (0.35–0.49), moderate (0.5–0.79), and strong (≥0.8).[27]

GAS for WD scores at first visit and a subsequent visit ~3 months later were used to measure **responsiveness** using Cohen's effect size, for both treatment naïve patients and those on treatment. As an external measure, the responsiveness of two standard global disability scales (SS3 and CGI item 1) was assessed for the same patient population. Cohen's effect size values were defined conventionally as small (0.2–0.49), moderate (0.5–0.79), and large (≥0.8).[28]

RESULTS

Thirty patients with WD (17 males, 13 females; mean age 17; range 7–40 years) from 23 unrelated families were studied. Twenty two were symptomatic and eight presymptomatic (supplementary data). All patients received pencillamine.

Reliability

The two raters required ~15 min to administer each tier, excluding time spent in review of medical records at baseline visit and laboratory tests. There was high to perfect inter-rater agreement between the two raters (ICC (A, 2): 0.96–1.0) (supplementary data). Since the observed inter-rater reliability was high, intra-rater reliability was not assessed.[25]

The four Tier 1 domain scores were weakly correlated with each other (Table 2). The Tier 2 total score had moderate to strong correlations with all Tier 1 domains except the Liver domain. Tier 2 exhibited good internal consistency with Cronbach's α of 0.89. Speech, Wilson's facies, posture and gait impairment, and dystonia had the strongest correlation with Tier 2 total score (Table 3). Factor analysis showed that the first seven factors accounted for 90.3% of the Tier 2 total score variance (first seven eigenvalues: 6.3, 2.0, 1.2, 1.1, 0.8, 0.7, and 0.5). The first factor was well-matched with the sum of all the items excluding psychosis and chorea; the latter two, however, were heavily weighted in the second factor.

Validity

The Tier 1 scores for the four domains, and the Tier 2 scores for the 14 items covered the rating ranges (supplementary data). The strong correlation of, (i) Cognition and behavior disability with UPDRS I; (ii) Motor disability and Tier 2 total score with UPDRS III; and the moderate correlation of, (i) Liver disability with Child Pugh scale and, (ii) Tier 2 total score with UPDRS I, establishes the convergent validity for these components of the scale (Table 4). The Tier 1 Liver and Motor domains and, Tier 2 total score were moderately correlated with the global disability scales, indicating that they were the main contributors to overall WD-related disability.

TABLE 3. *Spearman's rank correlation coefficients for the 14 Tier 2 items and the Tier 2 total score (n = 30)*

	Scholastic performance	Depression	Psychosis	Dystonia	Tremor	Chorea	Parkinsonism	Speech	Swallowing	Salivation	Posture & gait	KF rings	Uncommon	Tier 2 total
Wilson's facies	0.70*	0.28	0.40***	0.75*	0.29	0.12	0.50**	0.86*	0.59*	0.67*	0.85*	0.45***	0.42***	0.88*
Scholastic performance	1.00	0.33	0.57*	0.59*	0.01	0.16	0.29	0.61*	0.18	0.49**	0.69*	0.38***	0.21	0.68*
Depression		1.00	0.02	0.14	0.05	0.309	0.14	0.15	0.16	0.28	0.20	0.27	0.11	0.33
Psychosis			1.00	0.25	−0.09	0.303	−0.09	0.44**	−0.11	0.31	0.33	0.30*	0.46***	0.45***
Dystonia				1.00	0.50**	0.00	0.53**	0.82*	0.58*	0.52**	0.84*	0.34	0.42***	0.86*
Tremor					1.00	−0.16	0.39***	0.43**	0.57**	0.40***	0.30	0.39***	0.17	0.51**
Chorea						1.00	−0.01	0.10	−0.20	0.02	0.10	0.20	0.10	0.20
Parkinsonism							1.00	0.60*	0.67*	0.27*	0.57*	0.13	0.08	0.57**
Speech								1.00	0.64*	0.61*	0.87*	0.42***	0.55**	0.90*
Swallowing									1.00	0.41***	0.61*	0.42**	0.34	0.63*
Salivation										1.00	0.69*	0.57**	0.39***	0.72*
Posture & gait											1.00	0.40***	0.45***	0.87*
KF rings												1.00	0.31	0.64*
Uncommon													1.00	0.52**

*$P < 0.001$
**$P = 0.001$–0.01
***$P = 0.01$–0.05.

Responsiveness

Three months following the first assessment, 19 patients were stable, seven had improved and four had deteriorated, as assessed using CGI item 2. The Cohen's effect size for GAS for WD subscores corresponding to this period were roughly comparable with those of the two standard global disability scales, SS3 and CGI item 1. As expected, the GAS for WD scores and the global disability scores for treatment naïve ($n = 9$) patients showed greater variation between visits (larger Cohen's effect size), compared with patients already on treatment ($n = 21$). The greatest disparity in responsiveness between the two patient classes was seen in the Motor domain. Liver domain scores did not change over the observed period (Table 5).

DISCUSSION

Motivation and Existing WD Scales

WD is a treatable metabolic disease. Nevertheless, it is associated with considerable morbidity and mortality due to, in part, difficulty in monitoring treatment.[1,5,6,16] The challenge has been to develop a WD-specific scale that captures its multisystemic disability, is easily administrable and yet is sensitive to small clinical change. Till date there is no WD scale in use that fulfils these requirements. Drug trials and retrospective clinical studies have relied on proxy scales (Hoehn and Yahr and the UPDRS scales for Parkinson's disease, Unified Huntington's Disease Rating Scale etc.),[7–9] which have the significant short-coming of not capturing the distinctive and complex multisystemic spectrum of WD while including features not relevant to the disease.

A few WD scales have been developed for specific clinical application, such as identifying patients with WD who require liver transplant (Nazer et al.[10]; Dhawan et al.[11,12]) or to retrospectively assess impact of liver transplant on neurological function (Medici et.al.[13]). However, such domain specific scales have limited applicability outside the target population, or for monitoring patients in routine clinical practice.

In 2007, Członkowska et al., developed the Unified Wilson's Disease Rating Scale (UWDRS), which is a neurological (mainly motor) impairment scale and demonstrated good inter-rater reliability.[14] Leinweber et al., expanded UWDRS to include psychiatric and hepatic subscales and an item for osteoporosis or joint involvement.[15] The authors have administered UWRDS in a cohort of stable patients with WD over 12 years of age and reported good inter-rater reliability, internal consistency, and construct validity using earning capacity as

TABLE 4. *Convergent validity: Correlations between GAS for WD subscores and related scales (n = 30)*

		Child Pugh	UPDRS I[a]	UPDRS III[a]	SS3[b]	CGI item 1[c]
Tier 1 domains	Liver	0.65*	–	–	0.65*	0.70*
	Cognition & behaviour	–	0.85*	–	0.44***	0.33
	Motor	–	–	0.88*	0.62*	0.49**
	Osseomuscular	–	–	0.46***	0.34*	0.31
Tier 2	Total score	–	0.65*	0.91*	0.64*	0.54**

*$P < 0.001$
**$P = 0.001$–0.01
***$P = 0.01$–0.05
[a]Unified Parkinson's Disease Rating Scale (UPDRS) part I (mental dysfunction) and part III (motor examination).
[b]Three-point Severity Scale.
[c]Clinician Global Impression item 1.

an external measure. The reliance of UWDRS on clinical assessments alone limits its sensitivity to early liver involvement, which is usually subclinical. Responsiveness of UWDRS has not been reported.

GAS for WD is a multisystemic WD-specific scale designed for use in routine clinical practice to assess and track patients with WD. We discuss the design of the scale, observations from the pilot validation study, and outline the limitations of the scale.

Scale Design

The scale has a two-tier design. Tier 1 is a global disability measure of the disease burden across the four affected systems. The Tier 1 scores identify systems most affected by WD and aid in directing medical attention. Tier 1 can be administered by a clinician familiar with WD, and does not require specialist knowledge. This is particularly advantageous in geographical regions or clinical settings where specialist care may be limited.

Liver and neurological dysfunction have the largest impact on patient disability; however, the latter is more responsive to treatment and provides a sensitive index for monitoring disease progression. Therefore, Tier 2 is designed as a multidimensional neurological scale to increase the sensitivity of GAS for WD. It is best administered by neurologists though, with training, internists, and other specialists familiar with WD may be able to administer it reliably.

Tier 1: Global Disability.

The four Tier 1 domains individually represent four distinct phenotypes (video cases 1–4) of WD and collectively capture its complex multisystemic manifestation. The extent to which each of these domains is affected varies widely between patients. For example, patient 19 (video case 1) had life threatening liver disease but normal motor, cognition, and osseomuscular function (Tier 1 score: L5, C0, M0, O0) illustrating the clinical heterogeneity of WD, which in this patient, damaged the liver but spared other systems.

The ***liver domain*** in GAS for WD stratifies WD-related liver disease based on the mode and the urgency of therapeutic intervention required. Notably, the domain captures subclinical liver dysfunction, such as episode(s) of fleeting jaundice or nonspecific abnormal-

TABLE 5. *Three month responsiveness (Cohen's effect size) of GAS for WD subscores and standard global disability scales*

		Treatment naïve ($n = 9$)	On treatment ($n = 21$)
Tier 1 domains	Liver	0	0
	Cognition & behaviour	0.54	0.45
	Motor	0.78	0.14
	Osseomuscular	0.19	0.16
Tier 2	Total score	0.69	0.12
SS3[a]		0.73	0
CGI item 1[b]		0.46	0.18

[a]Three-point Severity Scale.
[b]Clinician Global Impression item 1.

ities in LFT that are common in children, but overlooked by existing scales. Copper chelation at these subclinical or early stages of liver involvement can arrest their progression to cirrhosis, which is both irreversible and the leading cause of death from WD.[1]

Cognition and behavioral problems and ***motor*** disability respond well to copper chelation, and are useful for tracking WD (Table 5; video case 5). Cognition and behavioral symptoms are often masked by overwhelming motor symptoms, or, if mild, dismissed as teenage problems. Serious behavioral problems invariably lead to poor drug compliance, and conversely, worsening behavioral scores suggest poor drug compliance, reinforcing the importance of tracking the cognition and behavioral scores independent of motor dysfunction.

Osseomuscular problems include nosologically ill-defined, and poorly classified spectrum of skeletal and muscle abnormalities that are frequent (seen in 40–75% of all patients with WD) and often lead to severe disability.[1,4] The pathogenesis of osseomuscular problems and their response to decoppering is yet unclear. By defining and grading osseomuscular disability, GAS for WD will enable their systematic study.

Tier 2: Neurological Assessment.

Tier 2 is a fine grained evaluation of neurological dysfunction due to WD. It is the first scale that grades two WD-specific clinical signs:

- KF rings[1]
- WD facies: Patients with WD develop a characteristic facial appearance with a distinctive dull look that is not seen in other movement disorders. Though reported,[2,18] this appearance has not previously been graded or correlated with other manifestations of WD. We term this look ***Wilson's facies*** and define it as a variable combination of open mouth, facetious smile, drooling saliva[2] and a dull look (pseudoptosis, decreased eye contact, decreased exploratory eye movements, drooping angle of mouth and delayed or no change in facial expression).

To capture WD's clinical heterogeneity, Tier 2 encompasses a range of neurological features, but an individual patient is unlikely to exhibit all the included dysfunction. The absent features are generally not affected by treatment and the corresponding scores do not change, which in effect, reduces the scale's responsiveness. Patient 16 (video case 3) for example, was mute and bedbound, had high scores in items such as dystonia, speech, posture and gait, but a zero score in chorea, salivation etc. Therefore, despite being severely disabled she had a total Tier 2 score of 32/56.

Clinical Observations

We validated GAS for WD in a pilot study of 30 patients with WD having a wide range of disabilities, ranging from presymptomatic (patients with mild disease) to severely disabled. The scale scores were reproducible and satisfied other measures of reliability. Comparison of GAS for WD subscores with scales used routinely in clinical practice and as end points in drug trials (Child Pugh scale, UPDRS, SS3 and CGI) demonstrated its validity. The scale was sensitive to clinical change (responsive) in both drug naïve patients and patients already on treatment. As discussed below, we were also able to track patterns (extent and time course) of treatment response in individual patients over the 1.5-year follow-up.

In our patients with WD liver and neurological disability had the greatest contribution to the overall disability. Four of the eight presymptomatic and 19/22 symptomatic patients with WD had cirrhosis. Of these, a majority (19/23) had compensated cirrhosis, which remained stable during the study period. Unlike liver disability, neurological disability showed improvement with decoppering in drug naïve patients, as is seen in the Cohen's effect sizes of related scores (Table 5) and in the videoclip (case 5). Even some patients on therapy who were presumed to have a "residual" neurological disability showed significant neurological improvement on increase in pencillamine dosage.

In our study, patients who were mute and bedbound (M4, M5) at start of treatment developed severe psychoses (C3–C5) in tandem with recovery of their motor function. We hypothesize that in these patients psychosis was masked by mutism and severe motor disability, and manifested once motor function improved. We call this phenomenon ***emergent psychosis***. Unlike neurological deterioration precipitated by sudden copper mobilization to brain following aggressive copper chelation,[29] patients with emergent psychosis benefited from continued decoppering. Similarly, patients with WD with serious psychosis, if untreated, developed severe motor disability and mutism that masked their psychosis; a phenomenon we term ***concealed psychosis.***

Various components of neurological dysfunction improved at differing rates on treatment. Improvement in WD facies was the earliest clinical change, seen within 3–5 months. WD facies resolved in parallel with neurological disability, making WD one of the

few neurological diseases with a *reversible dull look*. Reduction in KF rings was observed only after 8–12 months. Dystonia, gait and posture, and psychosis improved dramatically over 12–18 months, while speech recovered incompletely. Noncompliance for three or more consecutive months worsened neurological scores.

Two thirds (20/30) of the patients in our study had osseomuscular involvement. Of these, 14/30 had abnormal X-rays (O1). Interestingly, eight patients experienced recurrent fleeting pain and swelling in large joints that were ignored as growing bone pains. Osseomuscular disability did not show much variation over the observation period.

Scope and Limitations

The proposed scale is intended for use in routine clinical practice to objectively assess patients with WD and as an efficacy measure for interventional trials for treatment of WD. However, judging efficacy of interventions aimed specifically at individual components of WD, such as gait or swallowing may require use of more specialized scales.

Clinical signs and symptoms are very sensitive index of neurological dysfunction due to WD, while liver and osseomuscular involvement is frequently subclinical till later stages. Therefore, there is a trade-off between a purely clinical scale that misses early liver or osseomuscular involvement when interventions have a maximal impact and, a complex scale that includes specialized, expensive, or invasive investigations. To keep GAS for WD simple and practical we have relied on simple noninvasive tests (LFT, abdominal USG, and skeletal X-rays).

GAS for WD provides detailed anchors to delineate the gradation level for each domain and item; however, it may not always be possible to discern or classify the underlying cause for an observed disability or impairment. For example, motor disability may contaminate osseomuscular disability or obscure (mask) behavioral problems. Hence, as in other scales in medicine, we recommend the principle of grading "what you see" (Table 1).

In this pilot study, we have assessed the psychometric properties of GAS for WD with a limited sample size of 30 patients and two neurologists as raters. Larger multicentric studies with raters from different specialities and varying experience are needed to verify our results and observations. Moreover, raters who are less familiar with the scale may require greater time to administer the scale.

CONCLUSIONS

We propose a composite scale to quantify disability from WD. If the pilot study results are verified in larger trials, GAS for WD would be an invaluable tool for monitoring treatment in individual patients; ultimately reducing WD-related morbidity and mortality. Orderly assessment of GAS for WD scores over time and in varying patient populations would facilitate identification of different phenotypes of the disease, their natural history and, their (possibly diverse) response to treatment. Such studies would also aid in exploring and comparing various treatment regimens.

LEGENDS TO THE VIDEO

Cases 1–4 illustrate the 4 GAS for WD phenotypes (Liver, Cognition and behaviour, Motor and Osseomuscular). Case 5 illustrates that GAS for WD is sensitive to clinical change and tracks treatment response.

Acknowledgments: The project was funded by Jaslok Hospital and Research Center, Mumbai, India (431/27754). AA was supported by Parkinson's Disease Foundation of India.

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