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Letters to the Editor Related to Published Articles

Unverricht–Lundborg Disease—A Misnomer?

Chew et al.[1] studied the long-term natural history of Unverricht–Lundborg disease (ULD, progressive myoclonic epilepsy of Unverricht–Lundborg type, EPM1, OMIM #254800) in 8 patients with mutations in the cystatin B gene (*CSTB*).[1]

Working in the area of Southern Sweden where Herman Lundborg (1868–1953) described this disorder that now bears his name, I recently read in his publications.[2–4] From 1898 to 1910, Lundborg compiled information on 17 patients afflicted by this condition. They all belonged to one extensive kindred, the "Lister" family.

While Chew et al. reported dystonia as a new clinical feature of EPM1,[1] it struck me that Lundborg described symmetrical tremor and marked rigidity. Lundborg distinguished three stages of the disorder: Beginning in childhood or early adolescence, nocturnal attacks with involuntary symmetric muscle twitches occurred (stage 1). Patients were awake and conscious during the attacks, which often were painful, caused anxiety, and reminded Lundborg of clonic, tonic-clonic, or tetanic seizures. A few years later, diurnal tremor, myokymia, and myoclonic or dystonic muscle contractions appeared, marking stage 2. Typically, the contractions initially affected the upper extremities symmetrically, and subsequently involved lower extremities, head, and neck, and finally, all muscles under voluntary control. Reminding of startle responses, tactile and auditory stimuli elicited these involuntary muscle contractions. Psychological stress aggravated them. Symptom severity fluctuated markedly from day to day. Gradually, increased muscle tone was noted in the interval between attacks. Several years to some decades later, further progression lead to stage 3 symptoms: As the nocturnal attacks disappeared completely, daytime muscle contractions became more and more pronounced. Regularly, marked generalized rigidity developed, leaving some patients utterly stiffened in certain poses, incapable of any voluntary movements. Lundborg noted that the clinical picture of some of his patients in the terminal phase reminded him of paralysis agitans (Parkinson's disease).[2]

In contrast, tremor and rigidity are not mentioned in the other historical description of EPM1 by Unverricht,[5,6] or in patients with PME and *CSTB*-mutations.[1] Neither are these symptoms included in the 1990 diagnostic criteria for progressive myoclonic epilepsy of Unverricht–Lundborg type according to the Marseille consensus group[7] nor in Chew's case series.[1]

Chew mentions rapidly progressing dementia and other psychiatric symptoms such as depression, emotional lability, impulsive personality disorder, or aggressive behavior in some of the 8 EPM1 patients.[1] In vivid language, Lundborg described visual hallucinations and behavioral disturbances in some of the patients.[2–4] Cognitive decline was very variable in Lundborg's patients, although vigilance was decreased during motor attacks.

The important discovery that *CSTB* mutations are associated with ULD was made in Finland,[8–10] which has the world's highest incidence of this disease (1:20,000). Unverricht had described 8 patients in Tartu, now Estonia.[5,6] The Baltic population of Estonia is genetically closely related to Finns, as analyses of mitochondrial DNA, transferrin variants, and X-chromosomes have shown.[11–13] Unverricht's patients from Estonia and *CSTB*-positive cases from Finland shared the same clinical symptoms. However, the genetic distance between Swedes and Finns/Balts is longer, which may support the notion that the disease described by Lundborg in Sweden is different. No epidemiological data are available from Sweden, but in neighboring (also genetically) Denmark the incidence is ~27-fold lower than in Finland.

Much of the recent genetic and clinical research on ULD was performed in Finland, where ULD patients usually have *CSTB*-mutations. In fact, the presence of a *CSTB* mutation is today considered a prerequisite for the diagnosis of ULD,[14–16] which has probably shifted boundaries of disease definition. However, comparison of historical and contemporary sources suggests that the disorder described by Lundborg differs from the entity nowadays referred to as ULD.

Historically, Lundborg later promoted the concept that the Swedish race threatened to degenerate. Among the 2,232 individuals in this work from 1913,[4] he classified 15% as "morally or socially inferior" (e.g., "alcoholic," "criminal," "wanton," "of bad character") and another 9.5% as "psychiatrically inferior." Lundborg was appointed as professor for Racial Hygiene, and he advocated the ideology of race biology. His influence contributed to the implementation of forced sterilization programs in Sweden.

If Unverricht and Lundborg described different entities, the expression "Unverricht–Lundborgs disease" becomes questionable. A designation such as "progressive myoclonus" for the entity described by Lundborg is perhaps more ideologically neutral, and allows the term EPM1 to remain reserved for patients with confirmed *CSTB* mutation.

Although I cannot agree to Lundborg's ideological views later in life, his meticulous data collection was accurate, and I think he was correct in his 1901 discussion on the wide array of disorders with myoclonus when stating that "one researcher does not seem to mean quite the same as the other."[2]

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Reply: Puschmann "Unverricht-Lundborg Disease—A Misnomer"

On behalf of all the authors of the paper: "The natural history of Unverricht Lundborg disease: A report of eight genetically proven cases,"[1] we would like to thank Dr. Puschmann for his interest in our paper and his comments.[2]

We stand educated by Dr. Puschmann's detailed and fascinating account of the original work of Lundborg and Unverricht. We entirely agree that the disorder that now bears their names is in many ways far removed from their original descriptions, leaving aside the additional confusion generated by the fact that Unverricht and Lundborg may indeed have been describing different entities. We were also not aware of Lundborg's rather challenging social views. The issues of variable phenotype, misattribution, and moral ambiguity are difficulties that face many eponymous syndromes.

Genetic advances such as the discovery of the cystatin B mutation allow a reappraisal of formally clinically defined entities, and this was our intention in describing eight genetically characterized patients. Further description of genetically characterized cases (including perhaps genetic investigation of relatives from the original families) will enhance our knowledge of the phenotypic range of the disorder. We agree with Dr. Puschmann that this process may lead to a rethink on the appropriateness of the term "Unverricht-Lundborg disease" to describe this condition.

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Comment on "Individualized Assessment of Quality of Life in Idiopathic Parkinson's Disease"

We read with interest the recent article by Lee et al.[1] regarding the use of the Schedule for Evaluation of Individual Quality of Life Direct Weighting (SEIQoL-DW) in Idiopathic Parkinson's disease (PD). The SEIQoL-DW is a semistructured interview with three steps: (1) patients indicate the five most important areas of their life (domains); (2) rate how well each domain is functioning; and (3) rate the relative importance of each domain on a weighting wheel.[2] Lee et al.[1] found that the SEIQoL-DW index was predicted by depression and by psychosocial domains of the Parkinson's Disease Questionnaire (PDQ-39), the most commonly used tool for evaluating Health Related Quality of Life (HRQoL) in PD.[3]

To evaluate the usefulness of the SEIQoL-DW in our clinical research, we conducted a pilot study of 20 PD patients to compare the usefulness of the SEIQoL-DW[2] to a standar-

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TABLE 1. *Clinical and demographic characteristics of study group*

Clinical characteristics	
Male, *n* (%)	13 (65%)
Age, (yr); median (range)[a]	69.5 (54–87)
Age at symptom onset, (yr); median (range)	60.0 (44–83)
Disease duration, (yr); median (range)[b]	6.5 (1–23)
Hoehn and Yahr, median (range)	2.0 (2.0–4.0)
MMSE, median (range)[c]	29 (25–30)
SDS median (range)[d]	41 (21–50)
Motor symptoms, median (range)[e]	
Resting tremor	2 (0–4)
Rigidity	2 (0–3)
Bradykinesia	2 (1–4)
Taking Levodopa, *n* (%)[a]	12 (60.0%)
Dose Levodopa, mean (SD)[a]	670.8 (460.5)
Demographic profile, n (%)[a]	
Married	15 (83.3%)
Living with one or more people	15 (83.3%)
Retired	12 (66.7%)
Income of $40,000 or less	6 (46.1%)
Education level	
High School or below	9 (50.0%)
Bachelor's Degree or higher	5 (27.8%)

[a]At the time of interview.
[b]Disease duration from onset to time of interview.
[c]Min-Mental State Examination (range of possible scores 0–30)
[d]Zung Self-Reported Depression Scale (range of possible scores 20-80; <40 no symptomatology, 40–47 mild depressive state, 48–55 moderate depressive state, and ≥ 56 severe depressive state).
[e]UPDRS Score.

dized questionnaire consisting of the PDQ-39,[4] Zung Depression Scale (SDS),[5] MOS-Social Support Scale (SSS),[6] and some demographic questions not typically acquired during routine clinic visits. Inclusion criteria were willingness to complete both the SEIQoL-DW and the questionnaire, MMSE score ≥24, no active psychiatric illness, and last clinical diagnosis of IPD. Patients took an average 27.5 min to complete the interview (range, 18–50). The clinical and demographic profile of the study group is presented in Table 1. In the SEIQoL-DW, the most frequently nominated domains were family (85.0%), health (60.0%), finances (50.0%), and social/leisure (45.0%). Although family and health domains were rated as having fairly close relative importance (*t*-test; $P = 0.10$), family domain was rated as having a higher level of functioning (Mann–Whitney, $P = 0.008$).

Demographic characteristics were not predictive of SEIQoL index or the PDQ-39 single index score. Multiple regression analyses of SEIQoL index with clinical characteristics revealed no significant predictors of QoL. On the other hand, multiple regression analysis of the PDQ-39 single index score with clinical variables revealed that H&Y and SDS score were significant predictors ($P = 0.0003$). The SEIQoL index was negatively correlated with the PDQ-39 single index score (Spearman's $r = -0.62$), and multiple regression modeling revealed that only social support and discomfort domains of the PDQ-39 predicted the SEIQoL index ($P = 0.02$). This indicates that as problems with social relationships and discomfort levels increase, perceived QoL, as measured by the SEIQoL index, decreases. Not surprisingly, the SSS total support index was also correlated with the SEIQoL index and the PDQ-39 single index score.

A significant portion of subjects (30%) required either some or complete physical assistance manipulating the weighting wheel. Half of these patients also required prompting to elicit five domains. Whether or not subjects required assistance was correlated with the severity of bradykinesia (Spearman's $r = 0.52$) and resting tremor (Spearman's $r = 0.34$), and the time required to complete the interview (Spearman's $r = 0.35$). Multiple regression analysis revealed that age and rigidity predicted the time required to complete the interview ($P < 0.0001$). This indicates that as subjects' age and as the severity of rigidity increases, more time will be required to complete the SEIQoL-DW interview.

We found that the PDQ-39 measures experiences of health status (HRQoL), whereas the SEIQoL-DW measures the more subjective and individualized aspects of QoL.[7] The SEIQoL index is more closely associated with the psychosocial domains of the PDQ-39. Additionally our analysis indicates that demographic factors do not predict either HRQoL or individual QoL. Although HRQoL was determined by global disability and depression, none of the clinical or demographic variables predicted individual QoL. The weaknesses of the SEIQoL-DW lie with eliciting domains, manipulating the weighting wheel, and the time required to complete the interview. As in previous investigations, we found a high proportion of participants who required assistance with the weighting wheel and/or eliciting domains.[7,8] The comments by Lee et al.[1] about the challenges using the SEIQoL-DW weighting wheel may be somewhat understated. Also, a discussion of the potential challenges eliciting the domains would have been informative. In PD, where global disability and symptom severity generally increase over time, it is likely that the frequency and severity of the aforementioned challenges of the SEIQoL-DW would increase. As such the usefulness of the current format of the SEIQoL-DW for prospective follow-up in PD is limited.

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Young Age Onset of Cervical Dystonia

Koukouni et al.[1] recently provided a potentially heuristically important observation regarding a segment of the cervical dystonia (CD) population with onset of symptoms prior to the age of 28 years, in which family history of dystonia, male gender, and frequency of remission were distinctive, perhaps representing a genetically determined subgroup.

Intrigued with their observation, I revisited the data set of one of their references, a personal experience with 347 referred CD patients seen while on staff at Mayo Clinic, Rochester, MN (1969–1985),[2] and then analyzed data collected on 305 patients evaluated by me at the Arizona Dystonia Institute/Arizona State University (1987–2007), examining features of CD patients in each sample with onset of symptoms prior to the age of 30 years.

Tables 1 and 2 summarize the observations that reinforce many of the above authors' findings. Compared with older age onset CD patients, younger age onset CD patients are more apt to the following:

- Experience a remission, which will likely relapse.
- If extra nuchal sites are involved, they are more apt to have brachial than cranial involvement with chin turning toward the affected upper limb.
- Have a higher frequency of history of a first-degree relative with dystonia (see also Table 1[3]).
- Not uncommonly, have X-ray evidence of scoliosis.

Although both groups have more females than males, a greater percentage of males is seen in early onset CD.

However, although young age onset CD patients have a high rate of psychiatric symptoms pre-onset, and subsequently, the frequency is no greater than that of older age onset CD patients (see also[3]). Physical trauma antecedent to onset is no more frequent than in older age onset CD patients (see also[4]). Like older CD patients, head tremor, when present, is more common in female early onset CD patients.[5,6]

These findings, from two additional large patient series, reinforce the possibility of a meaningful nosologic entity within the CD population, perhaps genetically determined.

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TABLE 1. *Summary of demographic, clinical details, investigations, and comparison of patients with cervical dystonia onset at less than 30 years of age versus greater than 30 years of age derived from Duane, 1988*[2]

Demographic, clinical details, and investigations	<30-yr old onset	>30-yr old onset	*P**
Number of patients	47 (13% of total N)	300 (87% of total N)	
Male	21 (45% of young pop)	111 (37% of older pop)	NS
Female	26	189	
Mean age of onset in years (range)	21 (5–29)	44 (30–72)	
Family history of dystonia	12 (25%)	33 (18%)	<0.0001
Family history of tremor	15 (32%)	114 (38%)	NS
Past medical history			
Depression and/or anxiety	19 (40%)	108 (36%)	
Head, neck or shoulder injury			
≤12 months before onset	7 (15%)	54 (18%)	
Neck surgery	6 (13%)	27 (9%)	
History of remission	20 (43%)	18 (6%)	<0.0001
Extranuchal sites			
Cranial	4 (9%)	79 (26%)	0.0001
Brachial	8 (17%)	14 (5%)	0.0005
	(7 head rotated toward affected limb)	(10 head rotated toward affected limb)	
Head tremor	12 [3 male] (26%)	87 [10 male] (29%)	
Hand tremor	8 (17%)	15 (5%)	
X-ray entire spine scoliosis			
Present/Performed	9/24 (38%)	21/47 (45%)	NS

*Chi square.

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TABLE 2. *Summary of demographic, clinical details, investigations and comparison of patients with cervical dystonia onset at less than 30 years of age versus greater than 30 years of age at the Arizona Dystonia Institute*

Demographic, clinical details, and investigations	<30-yr old onset	>30-yr old onset	*P**
Number of patients	28 (9% of total)	277 (91% of total)	
Male	13 (46%)	85 (31%)	0.0891[a]
Female	15 (54%)	192 (69%)	
Mean age of onset in years (range)	21 (5–29)	45 (30–73)	
Family history of dystonia	6 (21%)	39 (14%)	0.2960[b]
Family history of tremor	11 (39%)	127 (46%)	
Past medical history			
Depression and/or anxiety	6 (21%)	85 (31%)	
Head, neck or shoulder injury			
≤12 months before onset	5 (18%)	61 (20%)	
Neck surgery	1 (4%)	23 (8%)	
Depression present	12 (43%)	188 (68%)	
History of remission	8 (29%)	33 (12%)	0.0137[c]
Extranuchal sites			
Cranial	3 (11%)	54 (19%)	
Brachial	4 (14%)	13 (5%)	0.0349[d]
Manual	11 (39%)	88 (32%)	
Axial	4 (14%)	21 (8%)	
Only head tremor	7 [1 male] (25%)	97 [13 males] (35%)	
Only hand tremor	3 [2 males] (11%)	6 [4 males] (2%)	
Both head and hand tremor	2 [1 male] (7%)	73 [39 males] (26%)	
X-ray entire spine scoliosis			
Present/Performed	8/28 (29%)	36/237 (15%)	0.0719[e]
MRI head			
Normal/Performed	4/4	67/72 (1 only structural)	
Dyt 1			
Normal/Performed	4/4	0/0	

*Chi square.
[a]Combined 1998 and 2007: $p=0.04$.
[b]$P < 0.0001$.
[c]$P < 0.0001$.
[d]$P < 0.0001$.
[e]$P = 0.05$.

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