Published Ahead of Print on January 19, 2018 as 10.1212/WNL.0000000000004996

ARTICLE OPEN ACCESS

Electrophysiologic testing aids diagnosis and subtyping of myoclonus

Rodi Zutt, MD, Jan W. Elting, MD, PhD, Jonathan C. van Zijl, MD, J. Han van der Hoeven, MD, PhD, Christiaan M. Roosendaal, MD, Jeannette M. Gelauff, MD, Kathryn J. Peall, MD, PhD, and Marina A.J. Tijssen, MD, PhD

Correspondence
Dr. Tijssen
m.a.j.de.koning-tijssen@umcg.nl

Neurology® 2018;90:1-11. doi:10.1212/WNL.0000000000004996

Abstract

Objective

To determine the contribution of electrophysiologic testing in the diagnosis and anatomical classification of myoclonus.

Methods

Participants with a clinical diagnosis of myoclonus were prospectively recruited, each undergoing a videotaped clinical examination and battery of electrophysiologic tests. The diagnosis of myoclonus and its subtype was reviewed after 6 months in the context of the electrophysiologic findings and specialist review of the videotaped clinical examination.

Results

Seventy-two patients with myoclonus were recruited. Initial clinical anatomical classification included 25 patients with cortical myoclonus, 7 with subcortical myoclonus, 2 with spinal myoclonus, and 15 with functional myoclonic jerks. In 23 cases, clinical anatomical classification was not possible because of the complexity of the movement disorder. Electrophysiologic testing was completed in 66, with agreement of myoclonus in 60 (91%) and its subtype in 28 (47%) cases. Subsequent clinical review by a movement disorder specialist agreed with the electrophysiologic findings in 52 of 60; in the remaining 8, electrophysiologic testing was inconclusive.

Conclusions

Electrophysiologic testing is an important additional tool in the diagnosis and anatomical classification of myoclonus, also aiding in decision-making regarding therapeutic management. Further development of testing criteria is necessary to optimize its use in clinical practice.

From the Department of Neurology (R.Z., J.W.E., J.C.v.Z., J.H.v.d.H., C.M.R., J.M.G., M.A.J.T.), University Medical Center Groningen, University of Groningen, the Netherlands; and Neuroscience and Mental Health Research Institute (K.J.P.), Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, UK.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by Research Councils UK.

Glossary

CHAID = Chi-squared Automatic Interaction Detection; **CM** = cortical myoclonus; **CS** = cortical spike; **FJ** = functional jerks; **GCI-S** = Global Clinical Impression–Severity; **ICC** = intraclass correlation coefficient; **MMS** = multiple myoclonus subtype; **PM** = peripheral myoclonus; **SCM** = subcortical myoclonus; **SM** = spinal myoclonus; **SSEP** = somatosensory evoked potential; **UMRS** = Unified Myoclonus Rating Scale.

Myoclonus is a frequently observed hyperkinetic movement disorder, which is often classified according to its anatomical origin: cortical myoclonus (CM), subcortical myoclonus (SCM), spinal myoclonus (SM), peripheral myoclonus (PM), or functional jerks (FJ) in case of a functional movement disorder.

Electrophysiologic testing is frequently useful in distinguishing myoclonus from other hyperkinetic movement disorders, and in identifying its anatomical origin.[1–3] The tests used in the assessment of myoclonus include polymyography, EEG-EMG back-averaging, coherence analysis, and somatosensory evoked potential (SSEP).[4–8] Table 1 summarizes the electrophysiologic criteria used in the diagnosis of myoclonus and its subtypes.

The sensitivity and specificity of electrophysiologic testing in patients with myoclonus are largely unknown, with the majority of work to date being limited by small cohorts, highly selected patient populations, or reliance on expert opinion to determine the diagnosis.[9–11]

Our recent retrospective analysis of 85 patients with myoclonus demonstrated the key clinical and electrophysiologic features in distinguishing myoclonus subtypes.[12] In 74% of cases, the clinical diagnosis of myoclonus was confirmed with electrophysiologic testing, and electrophysiologic assessment of the myoclonus subtype aided diagnosis in 73% of cases. In this study, we sought to apply these principles to a prospectively recruited cohort of patients, evaluating the contribution of electrophysiologic testing in the diagnosis and management of myoclonus.

Methods

Participants

Participants with a clinical diagnosis of myoclonus were identified prospectively from inpatient and outpatient settings (July 2014 to June 2016). Exclusion criteria included ongoing inpatient care on the intensive care unit, language and/or literacy barriers, and age 6 years or younger. All participants were followed up for a minimum of 6 months, after which a final diagnosis was made.

Initial clinical classification

The initial clinical diagnosis of myoclonus and its anatomical subtype was provided by the participants' primary caring neurologist (adult or pediatric), with all participants undergoing a standardized and systematic assessment, including videotaped clinical examination.

Electrophysiologic testing

The standardized electrophysiologic protocol included an initial polymyography, with participants excluded at this stage if the myoclonus was too subtle to adequately perform the assessment. For those meeting electrophysiologic criteria for myoclonus, further investigations included EEG-EMG back-averaging (if >25 jerks) or coherence analysis (if jerk frequency was >3 Hz). Where possible, those with CM and SCM underwent testing for SSEPs (figure e-1, http://links.lww.com/WNL/A164).

An experienced neurophysiologist (J.W.E. and J.H.v.d.H.) blinded to the original clinical diagnosis determined whether the findings were consistent with myoclonus, and the likely myoclonus subtype. Table 1 summarizes the electrophysiologic criteria used in determining diagnosis.[12]

Diagnostic review and 6-month follow-up

A neurologist with expertise in movement disorders (M.A.J.T.), blinded to the initial diagnoses, reviewed the clinical details, videotaped clinical examination, and results of the electrophysiologic testing. Each patient was reviewed again 6 months after their initial assessment to determine any changes to the clinical findings, with the final diagnosis being confirmed by the specialist (figure 1).

Severity of the myoclonus

The severity of the myoclonus was determined by 2 independent clinicians (R.Z. and J.C.v.Z. or J.M.G.) following review of the videotaped clinical examinations, scoring sections 2 and 4 of the Unified Myoclonus Rating Scale (UMRS), and the 7-point Global Clinical Impression–Severity (GCI-S) scale.

Power analysis

A power calculation was performed based on our previously reported retrospective analysis.[12] It was estimated that electrophysiologic testing would support the clinical diagnosis of the myoclonus anatomical subtype in approximately 70%. A change in clinical classification of >20%, due to electrophysiologic testing, was considered clinically relevant. Using the One Proportion Confidence Interval Formula: Exact (Clopper-Pearson), a 95% confidence level, 0.7 (proportion), 0.8 (upper limit), we estimated that a minimum of 56 participants would need to be recruited.

Statistical analysis

The clinical characteristics were analyzed using Kruskal-Wallis tests for continuous, nonnormally distributed data.

Table 1 Electrophysiologic criteria of myoclonus and to aid diagnosis by anatomical subtype[12]

Myoclonus/anatomical subtype	Video-polymyography	Back-averaging/coherence analysis/SSEP	Importance of criterion
Myoclonus	Abrupt muscle contraction or interruption of muscle activity		Required
	Synchronous contraction of agonist and antagonist muscles[8,19]		Supportive
Cortical myoclonus	Burst duration positive myoclonus <100 ms		Required
	Multifocal/focal distribution		Supportive
	Presence of negative myoclonus[8]		Supportive
		Positive cortical spike back-averaging: Presence of a "time locked" biphasic potential >2 SD above baseline on the contralateral motor cortex preceding the jerks seen on the EMG according to the conduction time of corticospinal pathways (arms 15–25 ms/legs ±40 ms)[8,20]	Diagnostic
		Positive corticomuscular coherence: Occurrence of significant corticomuscular coherence in the alpha and beta band with a phase difference consistent with a cortical generator[6,7,21]	Diagnostic
		Presence of a giant SSEP: The P27 and N35 peaks had large amplitudes >5 μV and had a suitable shape[20,22,23]	Diagnostic
Subcortical myoclonus			
Brainstem	Burst duration >100 ms		Supportive
	Simultaneous rostral and caudal muscle activation at brainstem level[24,25]		Required
M-D/other	Burst duration >100 ms		Supportive
	Presence of negative myoclonus		Supportive
	Do not meet criteria of other categories[26]		Required
Spinal myoclonus			
Segmental	Burst duration >100 ms		Supportive
	Distribution according to 1 or 2 contiguous spinal segments		Required
	Rhythmic (1–2/min to 240/min)		Supportive
Propriospinal	Burst duration >100 ms[20]		
	Initiation in mid thoracic segments followed by rostral and caudal activation[27,28]		Required
	Propagation with slow velocity (5–15 m/s) in cord[20]		Required
Peripheral myoclonus	Burst duration <50 ms		Required
	Large MUAPs		Supportive
	Minipolymyoclonus or fasciculations/ myokymia		Supportive
	Accompanied by weakness/atrophy[29]		Supportive

Continued

Table 1 Electrophysiologic criteria of myoclonus and to aid diagnosis by anatomical subtype[12] *(continued)*

Myoclonus/anatomical subtype	Video-polymyography	Back-averaging/coherence analysis/SSEP	Importance of criterion
Functional jerks	Variable muscle recruitment		Supportive
	Variable burst duration (>100 ms)		Supportive
	Distractibility and/or entrainment[1,30]		Supportive
		Presence of a Bereitschaftspotential: Presence of a clear slow negative electrical shift (>5 μV) over the central cortical areas that increased over time 1–2 s before movement onset[5,31]	Diagnostic

Abbreviations: M-D = myoclonus dystonia; MUAP = motor unit action potential; SSEP = somatosensory evoked potential.

Interrater reliability was assessed using the intraclass correlation coefficient (ICC) (2-way mixed, consistency, average measures),[13] or Cohen κ[14] where appropriate. A Chi-squared Automatic Interaction Detection (CHAID) (SPSS, IBM, Armonk, NY; parent nodes n < 3, child nodes n > 1) analysis was undertaken to generate a decision tree in order to quantify the importance of the clinical and electrophysiologic criteria in the diagnosis of the myoclonic subtypes.

Standard protocol approvals, registrations, and patient consents

Full written informed consent was obtained from all participants according to the Declaration of Helsinki. The study protocol was approved by the University Medical Centre Groningen ethics committee (M14.157933, approved July 2, 2014).

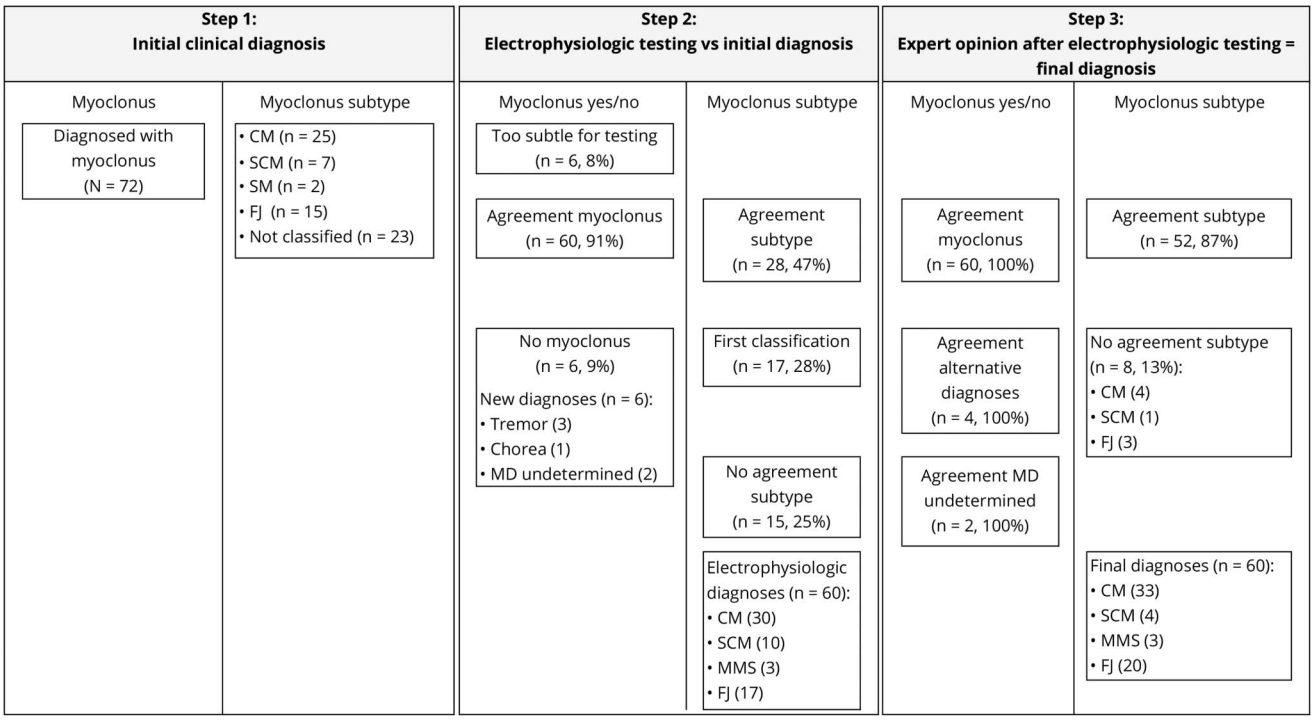
Results

Overall cohort

A total of 72 patients (32 male; 40 female) were recruited, with a median age of 29 years (range: 7–83 years), 59 from the outpatient setting and 13 from inpatient care.

The demographic details and clinical characteristics of this cohort are summarized in table 2 and table e-1 (http://links.lww.com/WNL/A165), respectively.

Figure 1 Overview of the stages of clinical assessment and diagnosis undertaken in this study



CM = cortical myoclonus; FJ = functional jerks; MD = movement disorder; MMS = multiple myoclonus subtypes; SCM = subcortical myoclonus; SM = spinal myoclonus.

Table 2 Demographic features of the myoclonus cohort

Demographic features	CM (n = 33)	SCM (n = 4)	FJ (n = 20)	MMS (n = 3)	Total (n = 60)
Sex, M/F	15/18	2/2	7/13	1/2	25/35
Age at examination, y[a]	21 (7–83)	18.5 (15–48)	31.5 (16–73)	63 (18–73)	22 (7–83)
Age at onset of myoclonus, y[a]	14 (0–83)	11 (10–14)	25 (12–66)	60 (4–73)	18 (0–83)
Follow-up interval, mo[b]	21	22	22	15	20
UMRS[a]					
Rest	9 (0–38)	14 (9–23)	17 (2–30)	9 (6–18)	11 (0–38)
Action	19 (6–57)	15 (7–23)	8 (0–33)	16 (0–31)	15 (0–57)
Total	31 (7–85)	31 (19–42)	23 (5–62)	28 (6–49)	27 (5–85)
GCI-S[a]	3 (2–7)	4 (3–5)	4 (2–6)	4 (3–5)	4 (2–7)
Family history of a related disorder	7	3	2	1	13
Other neurologic symptoms					
Eye movement disorder	8	0	0	0	8
Dystonia	9	4	0	1	14
Chorea	3	0	0	0	3
Ataxia	4	0	0	0	4
Comorbidity					
Psychiatric	5	0	4	0	9
Epilepsy	9	0	0	0	9
Cognitive problems	7	2	0	0	9
Liver or kidney disease	5	0	2	0	7
Structural damage to brain	3	0	1	0	4
Treatment					
No treatment	14	3	5	1	23
Clonazepam	9 (4)	0	0	2 (2)	11 (6)
Levetiracetam	9 (6)	0	0	0	9 (6)
Valproic acid	3 (1)	1 (0)	0	1 (0)	5 (1)
Multiple drug therapy	5 (4)	0	0	0	5 (4)
Physiotherapy	0	0	10 (5)	1 (1)	11 (6)
Explanation diagnosis	0 (0)	0 (0)	5 (5)	0 (0)	5 (5)
Side effects, yes/no					
Clonazepam	5/4	0/0	0/0	0/2	5/6
Levetiracetam	7/2	0/0	0/0	0/0	7/2
Valproic acid	3/0	0/1	0/0	0/1	3/2
Multiple drug therapy	3/2	0/0	0/0	0/0	3/2

Abbreviations: CM = cortical myoclonus; FJ = functional jerks; GCI-S = Global Clinical Impression–Severity; MMS = multiple myoclonus subtypes; SCM = subcortical myoclonus; UMRS = Unified Myoclonus Rating Scale.
Classification of myoclonus is given as the final diagnosis following review at 6 months post diagnosis. Treatment: the number in parentheses is the number of patients in whom the myoclonus improved with treatment.
[a] Values are displayed as median (range).
[b] Values are displayed as mean.

Clinical diagnosis of myoclonus pre-electrophysiologic testing

Of the 72 individuals with myoclonus, these were subdivided into CM (n = 25), SCM (n = 7), SM (n = 2), and FJ (n = 15), with subtype diagnoses not possible in 23 patients (32%) because of the complexity of the movement disorder.

Electrophysiologic diagnoses

In 6 patients (8%), clinically diagnosed with distal multifocal CM, the myoclonic jerks were of such small amplitude that the polymyographic recordings were indeterminate and unable to be interpreted. Of the remaining 66 patients, electrophysiologic testing supported a diagnosis of myoclonus in 60 (91%), with these subdivided into CM (n = 30), SCM (n = 10), multiple myoclonus subtypes (MMS) (n = 3), and FJ (n = 17). A cortical origin was detected in 5 of 9 patients (60%) with CM using back-averaging, and 16 of 20 (80%) using coherence analysis. SSEP analysis demonstrated giant potentials in 3 of 14 patients (21%) with CM, and a Bereitschaftspotential was identified in 5 of 12 patients (42%) with FJ.

A full summary of the electrophysiologic characteristics of this cohort can be seen in table 3.

Comparison of clinical and electrophysiologic diagnoses

There was agreement between the clinical diagnosis and electrophysiologic testing in a diagnosis of myoclonus for 91% (60/66) of the study cohort. Of these 60 cases, there was agreement of its subtype in 28 cases (47%) (14 CM, 2 SCM, and 12 FJ) and disagreement in 15 cases (25%). Of the remaining 17 cases (28%) without a clinical subclassification, electrophysiologic testing proved helpful, subdividing these into 12 CM, 2 SCM, and 3 FJ (table e-2, http://links.lww.com/WNL/A165).

Clinical opinion of the movement disorder specialist

There was agreement between the electrophysiologic testing and specialist movement disorder opinion in 66 cases, and agreement on its subtype in 52 of 60 cases (87%), considered a "substantial" agreement ($\kappa = 0.78$). A summary of the 8 cases in which there was disagreement between expert clinical diagnosis and electrophysiologic testing is provided in table 4; in each, there was a lack of conclusive electrophysiologic findings to facilitate a diagnosis of myoclonus subtype.

Final clinical diagnoses

Follow-up review after 6 months resulted in no changes to clinical diagnosis in all 60 patients, with the final subclassification including 33 CM (55%), 4 SCM (7%), 3 MMS (5%), and 20 FJ (33%). The CHAID analysis demonstrated (1) polymyographic measurement of the myoclonic burst duration, (2) exacerbation of the myoclonus with action, and (3) facial involvement to be the most important criteria in determining myoclonic subtype (figure e-2, http://links.lww.com/WNL/A164).

Severity of myoclonus

The median UMRS severity score was 27 (Rest 11/128, Action 15/144) and GCI-S score 4/7. No significant statistical difference was observed between the subtypes of myoclonus ($p = 0.2$). The interrater concordance was "excellent" (ICC = 0.94 [95% confidence interval: 0.9–0.96]) and "good" (ICC = 0.72 [95% confidence interval: 0.58–0.82]) for the UMRS and GCI-S, respectively.

Underlying etiology of the myoclonus

Of the 40 patients diagnosed with an organic movement disorder, an underlying etiology was identified in 21 patients (53%). In 12 patients, a causative genetic mutation was identified, and 9 were found to have an acquired cause including metabolic disturbances (n = 3), drug-induced myoclonus (n = 1), and structural brain lesions (n = 2). Of those with an underlying genetic etiology, the highest rate was among those with CM (n = 10), with mutations in the *NKX2.1* (n = 2) and *NPC1* (n = 2) genes being most common. A single case of a contiguous gene deletion (578 kb, 16p11.2) involving the *PRRT2* gene was identified with an extended phenotype including psychomotor retardation, hemiplegic migraine, epilepsy, myoclonus, and dystonia. All patients with a myoclonic epilepsy syndrome had evidence of epileptiform discharges on EEG, with the CM in those with juvenile myoclonic epilepsy and Lafora disease demonstrating an epileptic origin. All 4 patients with SCM had a clinical diagnosis of myoclonus dystonia, with a *RELN* variant identified in one patient. Table 5 summarizes the etiologic diagnoses and additional clinical characteristics.

Discussion

This prospective study has sought to demonstrate the benefit of electrophysiologic testing alongside clinical examination, in determining the diagnosis of myoclonus and its subtype in an unselected cohort. We have shown that this combined approach leads to changes in the initial diagnosis of myoclonus and its subtype in 53% of cases.

Overall, agreement of a diagnosis of myoclonus between the examining clinicians and the electrophysiologic findings was 91% (n = 60), decreasing to 47% (n = 28) with anatomical subtype. These findings contrast with results from similar studies in tremor cohorts (n = 210) where agreement between the 2 assessment forms was 87%, potentially reflecting greater clinical familiarity and larger patient cohorts.[15–17] We identified several clinical groups in which there was some consistency in the change in diagnosis following electrophysiologic testing. These included those with multifocal myoclonus (principally distinguishing between CM and SCM), combined movement disorders (e.g., myoclonus in the presence of dystonia), and functional jerks. The findings from this study also reflect the difficulty in determining a conclusive clinical diagnosis with myoclonus, and lend weight to the importance of electrophysiologic testing, particularly in nonspecialist centers.

Table 3 Electrophysiologic characteristics of each subtype based on the electrophysiologic findings

Electrophysiologic characteristics	CM	SCM	FJ	MMS	Total
No.	30	10	17	3	60
Type					
Positive	15	8	17	2	42
Negative	0	1	0	0	1
Both	15	1	0	1	17
Burst duration, ms					
30–50	2	0	0	1	3
50–100	27	2	0	1	30
50–200	0	5	1	1	7
100–300	0	1	3	0	4
>300	0	0	2	0	2
Variable	1	2	11	0	14
Distribution					
Focal	1	1	0	1	3
Multifocal	29	9	7	1	46
Segmental	0	0	0	1	1
Generalized	0	0	0	0	0
Variable	0	0	10	0	10
Back-averaging					
CS present	5	0	0	2	7
BP present	0	0	5	0	5
CS absent	4	3	0	0	7
BP absent	0	1	7	0	8
Not performed	15	1	0	1	17
Not possible	6	5	5	0	16
Positive coherence					
Present (segment sec)	16	0	0	0	16
Absent (segment sec)	4	4	0	1	9
Not performed	10	6	17	2	35
Giant SSEP					
Present	3	0	0	0	3
Absent	11	5	1	2	19
Not performed	13	5	15	1	34
Unable to interpret	3	0	1	0	4

Abbreviations: BP = Bereitschaftspotential; CM = cortical myoclonus; CS = cortical spike; FJ = functional jerks; MMS = multiple myoclonus subtype; SCM = subcortical myoclonus; SSEP = somatosensory evoked potential.

Higher-level electrophysiologic techniques were used to determine whether the myoclonus was of cortical origin or an FJ. The yield of back-averaging and coherence analysis to confirm a cortical origin was 60% and 80%, respectively. The additive value of these techniques was lower than the 100% seen in previous studies, potentially attributable to the heterogeneity

Table 4 Details of cases in which the clinical diagnosis changed after evaluation by the movement disorders specialist

No.	Age at onset, y[a]	Age at examination, y[a]	Clinical features	Electrophysiologic findings	Electrophysiologic diagnosis	Expert clinical diagnosis	Final clinical diagnosis	Reasons for revising the electrophysiologic diagnosis
1	10	20	Distal limbs and face	50–200 ms	SCM	CM	CM	Distal distribution
			Provocation by action	Back-averaging NP				Facial involvement
			Stimulus sensitive					Stimulus sensitivity
								No firm electrophysiologic results
2	0	10	Distal > proximal limbs	Positive and negative	SCM	CM	CM	Distal distribution
			Face	50–100 ms				Facial involvement
			Provocation by action	Back-averaging NP				Stimulus sensitivity
			Stimulus sensitive					No firm electrophysiologic results
3	69	69	Negative myoclonus	Negative	SCM	CM	CM	Negative myoclonus
			Distal limbs	50–100 ms				Metabolic derangements
			Provocation by action	Back-averaging NP				No firm electrophysiologic results
			Metabolic derangements					
4	6	7	Distal limbs	50–200 ms	SCM	CM	CM	Distal distribution
			Provocation by action	Negative back-averaging				Stimulus sensitivity
			Stimulus sensitive					Co-occurrence of epilepsy
			Epilepsy					No firm electrophysiologic results
5	16	17	Acute onset	50–200 ms	SCM	FJ	FJ	Acute onset
			Distal upper limbs	Negative back-averaging				Atypical sensory problems
			Entrainment					Entrainment
			Atypical sensory problems					No firm electrophysiologic results
6	18	18	Acute onset	Variable duration	SCM	FJ	FJ	Acute onset
			Distal limbs	Multifocal				Stimulus sensitive

Continued

Table 4 Details of cases in which the clinical diagnosis changed after evaluation by the movement disorders specialist *(continued)*

No.	Age at onset, y[a]	Age at examination, y[a]	Clinical features	Electrophysiologic findings	Electrophysiologic diagnosis	Expert clinical diagnosis	Final clinical diagnosis	Reasons for revising the electrophysiologic diagnosis
			Stimulus sensitive	Back-averaging NP				Change with distraction
			Change with distraction					No firm electrophysiologic results
7	20	20	Subacute onset	50–200 ms	SCM	FJ	FJ	Provocation by rest
			Proximal and distal	Negative back-averaging				Stimulus sensitive
			Provocation by rest					Change with distraction
			Stimulus sensitive					No firm electrophysiologic results
			Change with distraction					
8	14	20	Myoclonus, dystonia, tremor	Positive and negative	CM	SCM	SCM	Combined myoclonus and dystonia
			Cognitive difficulties	50–100 ms				No firm electrophysiologic results
			Proximal and distal	Back-averaging NP				

Abbreviations: CM = cortical myoclonus; FJ = functional jerks; NP = not performed; SCM = subcortical myoclonus.
[a] Values are displayed as median.

Table 5 Underlying etiologic diagnoses and additional clinical characteristics

Myoclonus subtype	Etiologic diagnosis or syndrome	Additional clinical characteristics	No.
CM (n= 33)	Juvenile Huntington (CAG repeat in *HTT* gene)	Cognitive impairment, severe epilepsy, spasticity	1
	Wilson disease (mutation *ATP7B* gene)	Parkinsonism, dystonia, ataxia, cognitive impairment	1
	Niemann-Pick type C (*NPC1* mutation)	Eye movement disorder, ataxia, dystonia (n = 1)	2
	Lafora disease (mutation *NHLRC1* gene)	Severe epilepsy, mild cognitive impairment	1
	Juvenile myoclonus epilepsy (no genetic mutation identified)	Epilepsy	1
	Myoclonus epilepsy (no genetic mutation identified)	Epilepsy, mild cognitive impairment	1
	Ramsay Hunt syndrome (*GOSR* mutation)	Ataxia, areflexia, eye movement disorder	1
	Ramsay Hunt syndrome (no genetic mutation identified)	Ataxia, areflexia, eye movement disorder	1
	Benign hereditary chorea (mutation *NKX2.1* gene)	Chorea, dystonia, areflexia	2
	Paroxysmal kinesigenic dyskinesia (16p11.2 deletion [578 kb], including the *PRRT2* gene)	Severe cognitive impairment, hemiplegic migraine, epilepsy, dystonia	1
	Myoclonus dystonia (18p11.21 deletion [14.9 Mb])	Dystonia	1
	Myoclonus dystonia (no genetic mutation identified)	Dystonia, bradykinesia (n = 1), eye movement disorder (n = 1)	2
	Medication-induced	Cognitive impairment (n = 1)	2
	Metabolic derangements due to liver or kidney disease	Cognitive impairment (n = 2), polyneuropathy (n = 1)	3
	Structural cerebral lesion	Mild cognitive impairment (n = 1), vascular parkinsonism (n = 1)	2
	Unknown		11
SCM (n = 4)	Myoclonus dystonia (*RELN* variant)	Dystonia	1
	Myoclonus dystonia (no genetic mutation identified)	Dystonia	3
	Unknown		0
MMS (n = 3)	Myoclonus dystonia (*RELN* variant)	Dystonia	1
	Creutzfeldt-Jakob disease	Cognitive impairment, stiffness	1
	Lumbar radiculopathy and FJ	Functional gait problem	1
	Unknown		0

Abbreviations: CM = cortical myoclonus; FJ = functional jerks; MMS = multiple myoclonus subtypes; SCM = subcortical myoclonus.

of our cohort in contrast to smaller, more selected study groups (n = 20/n = 3).[9,18] A CHAID analysis demonstrated that a combination of polymyography (burst duration) and clinical phenomenology provided the greatest accuracy (95%) in determining myoclonus subtype.

This study is limited by the lack of a definitive diagnostic test or marker. We have sought to reduce this by ensuring a minimum 6-month follow-up period to allow for any changes in clinical symptomatology. However, this lack of objective testing also serves to reinforce the potential gain of routine electrophysiologic testing to both aid, and provide additional evidence of the diagnosis of myoclonus and its subtype. Our cohort also likely reflects a more complex group of patients than might be expected in routine clinical practice, because of recruitment from a single specialist movement disorder center. We also acknowledge that while the electrophysiologic tests discussed are readily available within our center, such access varies considerably between centers and internationally.

Electrophysiologic testing is an important contributing diagnostic tool for the classification of myoclonus and its subtypes. While this clearly constitutes an important element of clinical work for neurologists with an interest in movement disorders, this algorithm of testing is also likely to be of use for those working in the fields of metabolic disorders, pediatrics, and epilepsy. Further development of the electrophysiologic criteria for myoclonus subtypes, and application of this work to larger, unselected patient cohorts is essential to improve its objectivity and diagnostic value.

Author contributions

R. Zutt: design of the study, collecting data, analysis and interpretation of the data, drafting and revising the manuscript. J.W. Elting: design of the study, collecting data, revising the manuscript. J.C. van Zijl: collecting data, revising the manuscript. J.H. van der Hoeven, C.M. Roosendaal, and J.M. Gelauff: collecting data, revising the manuscript. K.J. Peall: analysis and interpretation of the data, drafting and revising the manuscript. M.A.J. Tijssen: design of the study, collecting data, analysis and interpretation of the data, drafting and revising the manuscript.

Study funding

No targeted funding reported.

Disclosure

R. Zutt and J.W. Elting report no disclosures relevant to the manuscript. J.C. van Zijl is funded by the MD/PhD scholarship of the University of Groningen. J.H. van der Hoeven and C.M. Roosendaal report no disclosures relevant to the manuscript. J.M. Gelauff is funded by a scholarship from the Research School of Behavioural and Cognitive Neurosciences (BCN), part of the University of Groningen. K.J. Peall is funded by an MRC Clinician-Scientist Fellowship (MR/P008593/1). M.A.J. Tijssen is funded by STW Technology Society–NeuroSIPE, Netherlands Organization for Scientific Research–NWO Medium, Fonds NutsOhra, Prinses Beatrix Fonds, Gossweiler Foundation, Phelps Stichting, Stichting wetenschapsfonds dystonie vereniging, and educational grants from Ipsen, Allergan, Merz, Actelion, and Medtronic. Go to Neurology.org/N for full disclosures.

Received June 23, 2017. Accepted in final form November 20, 2017.

References

1. van der Salm SM, de Haan RJ, Cath DC, van Rootselaar AF, Tijssen MA. The eye of the beholder: inter-rater agreement among experts on psychogenic jerky movement disorders. J Neurol Neurosurg Psychiatry 2013;7:742–747.
2. Erro R, Bhatia KP, Edwards MJ, Farmer SF, Cordivari C. Clinical diagnosis of propriospinal myoclonus is unreliable: an electrophysiologic study. Mov Disord 2013;28:1868–1873.
3. Esposito M, Edwards MJ, Bhatia KP, Brown P, Cordivari C. Idiopathic spinal myoclonus: a clinical and neurophysiological assessment of a movement disorder of uncertain origin. Mov Disord 2009;24:2344–2349.
4. Shibasaki H, Nakamura M, Nishida S, Kakigi R, Ikeda A. Wave form decomposition of "giant SEP" and its computer model for scalp topography. Electroencephalogr Clin Neurophysiol 1990;77:286–294.
5. Shibasaki H, Hallett M. What is the Bereitschaftspotential? Clin Neurophysiol 2006;117:2341–2356.
6. Grosse P, Cassidy MJ, Brown P. EEG-EMG, MEG-EMG and EMG-EMG frequency analysis: physiological principles and clinical applications. Clin Neurophysiol 2002;113:1523–1531.
7. Brown P, Farmer SF, Halliday DM, Marsden J, Rosenberg JR. Coherent cortical and muscle discharge in cortical myoclonus. Brain 1999;122:461–472.
8. Shibasaki H, Yamashita Y, Kuroiwa Y. Electroencephalographic studies myoclonus. Brain 1978;101:447–460.
9. Caviness JN, Adler CH, Beach TG, Wetjen KL, Caselli RJ. Small-amplitude cortical myoclonus in Parkinson's disease: physiology and clinical observations. Mov Disord 2002;17:657–662.
10. Sinha S, Satishchandra P, Gayathri N, Yasha TC, Shankar SK. Progressive myoclonic epilepsy: a clinical, electrophysiological and pathological study from South India. J Neurol Sci 2007;252:16–23.
11. Binelli S, Agazzi P, Canafoglia L, et al. Myoclonus in Creutzfeldt-Jakob disease: polygraphic and video-electroencephalography assessment of 109 patients. Mov Disord 2010;25:2818–2827.
12. Zutt R, Elting JW, van der Hoeven JH, Lange F, Tijssen MA. Myoclonus subtypes in tertiary referral center: cortical myoclonus and functional jerks are common. Clin Neurophysiol 2017;128:253–259.
13. Fermanian J. Measuring agreement between 2 observers: a quantitative case [in French]. Rev Epidemiol Sante Publique 1984;32:408–413.
14. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–174.
15. Louis ED, Ottman R, Hauser WA. How common is the most common adult movement disorder? Estimates of the prevalence of essential tremor throughout the world. Mov Disord 1998;13:5–10.
16. Caviness JN, Alving LI, Maraganore DM, Black RA, McDonnell SK, Rocca WA. The incidence and prevalence of myoclonus in Olmsted County, Minnesota. Mayo Clin Proc 1999;74:565–569.
17. van der Stouwe AM, Elting JW, van der Hoeven JH, et al. How typical are "typical" tremor characteristics? Sensitivity and specificity of five tremor phenomena. Parkinsonism Relat Disord 2016;30:23–28.
18. Rossi Sebastiano D, Soliveri P, Panzica F, et al. Cortical myoclonus in childhood and juvenile onset Huntington's disease. Parkinsonism Relat Disord 2012;18:794–797.
19. Tassinari CA, Rubboli G, Shibasaki H. Neurophysiology of positive and negative myoclonus. Electroencephalogr Clin Neurophysiol 1998;107:181–195.
20. Shibasaki H, Hallett M. Electrophysiological studies of myoclonus. Muscle Nerve 2005;31:157–174.
21. Grosse P, Guerrini R, Parmeggiani L, Bonanni P, Pogosyan A, Brown P. Abnormal corticomuscular and intermuscular coupling in high-frequency rhythmic myoclonus. Brain 2003;126:326–342.
22. Shibasaki H, Yamashita Y, Neshige R, Tobimatsu S, Fukui R. Pathogenesis of giant somatosensory evoked potentials in progressive myoclonic epilepsy. Brain 1985;108:225–240.
23. Obeso JA, Rothwell JC, Marsden CD. Somatosensory evoked potentials in myoclonus. Adv Neurol 1986;43:373–384.
24. Bakker MJ, van Dijk JG, van den Maagdenberg AM, Tijssen MA. Startle syndromes. Lancet Neurol 2006;5:513–524.
25. Brown P, Rothwell JC, Thompson PD, Britton TC, Day BL, Marsden CD. The hyperekplexias and their relationship to the normal startle reflex. Brain 1991;114:1903–1928.
26. Marelli C, Canafoglia L, Zibordi F, et al. A neurophysiological study of myoclonus in patients with DYT11 myoclonus-dystonia syndrome. Mov Disord 2008;23:2041–2048.
27. Brown P, Thompson PD, Rothwell JC, Day BL, Marsden CD. Axial myoclonus of propriospinal origin. Brain 1991;114:197–214.
28. Brown P, Rothwell JC, Thompson PD, Marsden CD. Propriospinal myoclonus: evidence for spinal "pattern" generators in humans. Mov Disord 1994;9:571–576.
29. Zutt R, Elting JW, Tijssen MAJ. Myoclonus. In: Wolters Baumann EC, editors. Parkinson Disease and Other Movement Disorders. 1st ed. Amsterdam: VU University Press; 2014:513–533.
30. Hinson VK, Haren WB. Psychogenic movement disorders. Lancet Neurol 2006;5:695–700.
31. van der Salm SM, Tijssen MA, Koelman JH, van Rootselaar AF. The bereitschaftspotential in jerky movement disorders. J Neurol Neurosurg Psychiatry 2012;83:1162–1167.