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A Clinical Grading Scale to Predict Malignant Hyperthermia Susceptibility

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Background: **The diagnosis of an acute malignant hyperthermia reaction by clinical criteria can be difficult because of the nonspecific nature and variable incidence of many of the clinical signs and laboratory findings. Development of a standardized means for estimating the qualitative likelihood of malignant hyperthermia in a given patient without the use of specialized diagnostic testing would be useful for patient management and would promote research into improved means for diagnosing this disease.**

Methods: **Using the Delphi method and an international panel of 11 experts on malignant hyperthermia, a multifactor malignant hyperthermia clinical grading scale comprising standardized clinical diagnostic criteria was developed for classification of existing records and for application to new patients.**

Results: **This scale ranks the qualitative likelihood that an adverse anesthetic event represents malignant hyperthermia (malignant hyperthermia event rank) and that, with further investigation of family history, an individual patient will be diagnosed as malignant hyperthermia susceptible (malignant hyperthermia susceptibility rank). The assigned rank represents a lower bound on the likelihood of malignant hyperthermia. The clinical grading scale requires the anesthesiologist to judge whether specific clinical signs are appropriate for the patient's medical condition, anesthetic technique, and surgical procedure.**

Conclusions: **The malignant hyperthermia clinical grading scale is recommended for use as an aid to the objective definition of this disease. Its use may improve malignant hyperthermia research by allowing comparisons among well-defined groups of patients. This clinical grading system provides a new and comprehensive clinical case definition for the malignant hyperthermia syndrome. (Key words: Malignant hyperthermia: case definition; clinical grading scale; diagnostic criteria; epidemiology; susceptibility.)**

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MALIGNANT hyperthermia (MH) susceptibility is an uncommon inherited disorder of skeletal muscle in which commonly used anesthetics trigger sustained skeletal muscle hypermetabolism in patients who may have had no symptoms previously. First characterized in 1962,[1] MH presents with multiple nonspecific signs and laboratory findings of variable intensity and time course during and after exposure to anesthetic agents. These signs relate to skeletal muscle hypermetabolism and ischemia and their systemic sequelae and may include tachycardia, tachypnea, hypercarbia, respiratory acidosis, metabolic acidosis, masseter muscle rigidity, generalized muscular rigidity, myoglobinuria, rhabdomyolysis, arrhythmias, cyanosis, skin mottling, hyperkalemia, diaphoresis, rapid temperature elevation, hemodynamic instability, and coagulopathy.[2-4]

If an individual's MH susceptibility can be predicted before anesthetic administration, acute life-threatening MH events can be prevented through avoidance of MH-triggering medications. For many clinicians and researchers, MH has been a puzzling clinical entity, and there has been little agreement as to what constitutes a "true" MH episode. This lack of precise clinical definition has led to poor prediction of MH susceptibility because the diagnosis of an acute MH reaction by clinical criteria alone is not standardized and is difficult to perform, as a result of the nonspecific nature and variable incidence of many of the clinical signs and laboratory findings.[2,3]

Efforts to confirm MH susceptibility through laboratory testing began in 1970 with the development of the caffeine halothane contracture test.[5,6] That test requires an invasive muscle biopsy, and without the "gold standard" of a clear clinical definition of MH, the test's specificity and sensitivity are poorly estimated. Recent efforts in molecular biology[7-11] to identify the genetic markers of MH susceptibility likewise have been frustrated by the lack of agreed-upon methods of discriminating the clear cases from those that are less convincing.[12]

To improve MH susceptibility prediction, an international group of MH experts used the Delphi process to create a multifactor MH clinical grading scale that comprises standardized clinical diagnostic criteria. This grading scale ranks the likelihood that an adverse anesthetic event represents MH or, that with further investigation of family history, the patient sustaining the adverse anesthetic reaction will be diagnosed as MH susceptible.

Materials and Methods

To develop an international consensus for a standardized MH clinical grading scale, the anesthesiologist director of The North American Malignant Hyperthermia Registry (MGL) and a biostatistician (ARL) implemented the Delphi method, a system of polling opinions anonymously from an 11-member group of MH experts (the other authors), and of facilitating their consensus on the attributes of a MH event and the indicators of MH susceptibility. The Delphi process consists of a series of questionnaires completed by a panel of experts and a controlled feedback at each round in the form of the results of the prior round.[13,14] The process ends when the group approaches consensus or when sufficient information has been exchanged to achieve the goals of the process.[15] Feedback of information, and anonymous opinions of the experts, ensure that the panel considers a full range of ideas throughout the process. All communications were processed through a central office to ensure that opinions and scores could not be linked to individual experts.

The Delphi method was chosen because it obtains written opinions anonymously, thereby avoiding the potential for domination by the most assertive participants. Also, the Delphi method permits experts to respond and interact by mail or facsimile transmission over extended periods even when they are separated by long distances. MH experts were selected (by MGL) for their stature in the description and diagnosis of MH and were located in Australia, Canada, Denmark, United Kingdom, and the United States of America.

In brief, the consensus process proceeded as follows. Beginning with an initial set of proposed clinical indicators for judging MH events and MH susceptibility (supplied by MGL), experts were asked to identify a group of clinical indicators, to score the relative importance of these indicators, and to assemble the individual scores into a global raw score to rank the likelihood that an observed adverse anesthetic event represented an MH event. Each expert also modified the scoring system to rank the likelihood that a suspect individual was MH susceptible after a thorough investigation of the suspect family's anesthetic history. An individual's MH susceptibility was defined as the probability that an individual will experience an MH event if exposed to MH-triggering agents and the probability that an individual's blood relatives may also inherit the MH gene(s) in an autosomal dominant fashion. These

probabilities are not well defined, because MH-susceptible individuals do not consistently develop an MH event even after exposure to MH-triggering anesthetic agents, and penetrance is variable. Evidence of MH susceptibility could come from indicators applicable for MH events as well as from indicators taken from family history. The consensus process required seven separate written information exchanges over 18 months.

During the course of this study, the clinical indicators were refined as the result of comments from the expert group. For example, by the final information exchange, the initially proposed indicator "generalized muscular rigidity" was made more specific by excluding rigidity in the presence of shivering due to hypothermia and the shivering that is commonly seen during and immediately after emergence from inhalational general anesthesia. Similarly, the initially proposed indicator "reversal of MH signs with intravenous dantrolene" was refined to "rapid reversal of MH signs of metabolic and/or respiratory acidosis with intravenous dantrolene." Also, critical values for indicators such as increased creatine kinase (> 20,000 IU after an anesthetic that included succinylcholine; > 10,000 IU after an anesthetic without succinylcholine) were specified as a result of the group's interaction.

By the sixth information exchange, experts tested the prototype MH clinical grading scale by using it to rank the likelihood of MH events and MH susceptibility for hypothetical clinical case scenarios. Experts independently were able to apply the scoring rules to the six case scenarios with high consistency within scenario (coefficients of variation of 0.0–0.14 and standard deviations of 0–5.6 for the less complex cases and 15.8–17.2 for the two scenarios with many indicators present [*vide infra*]). The following is an example of a scenario in which all 11 MH experts judged an MH event "unlikely": a previously healthy patient received an anesthetic that included succinylcholine and developed ventricular tachycardia and a serum potassium of 8 mEq/l. In contrast, following is a scenario in which all 11 MH experts judged an individual to be "almost certainly" MH susceptible: a previously healthy patient received an anesthetic that included succinylcholine and controlled ventilation during which he developed generalized muscular rigidity without shivering, masseter spasm, inappropriate sinus tachycardia followed by ventricular tachycardia, an inappropriately increasing temperature of 40°C, end-expired carbon dioxide tension of 70 mmHg, arterial carbon dioxide tension of 75 mmHg, base excess −12 mEq/l, *p*H 6.90, serum potassium 8 mEq/l, serum creatine kinase 26,000 IU, and serum myoglobin 180 ng/ml. This patient's MH signs were reversed with intravenous dantrolene. The patient was subsequently discovered to have had a brother who had died of MH 15 yr earlier.

For the final information exchange, experts were instructed to evaluate 12 new scenarios selected from actual patient reports from the North American Malignant Hyperthermia Registry by assigning a rank of 1 ("almost never") to 6 ("almost certain") for the likelihood that the adverse anesthetic event represented MH or the likelihood that the patient was MH susceptible. Experts were asked to grade these scenarios with a rank of 1–6 by using their clinical judgment and referring, if needed, to the scoring instructions and indicator description, but *without* strictly applying the scoring system. After the deletion of one scenario, which an expert pointed out as badly flawed in description (rather than just difficult to interpret), the 11 sets of scores from each MH expert were compared and contrasted with the results of strict application (by MGL) of the scoring rules. Only 6 of 121 (6.6%) expert scores varied by more than one rank from that obtained through strict application of the scoring rules. See appendix 1. Statistical tests suggested good agreement among the experts: the intraclass correlation coefficient rating of 11 scenarios was 0.83 (95% confidence interval 0.75–0.92). Pairwise comparison of strict application of the scoring rules with the experts' scoring also revealed high levels of agreement for 10 of the 11 experts. See appendix 2.

The following is an example of a patient report scenario: a 31-year-old white woman was anesthetized for a nonemergent plastic surgical procedure with isoflurane and succinylcholine. Immediately after induction, she developed masseter spasm, slight tachycardia after two doses of atropine, and cola-colored urine. No arterial blood gas analysis results were reported. Six hours after induction, her creatine kinase was 22,800 IU. She was treated with volatile anesthetic discontinuation, hyperventilation, and fluid loading. The score of this scenario with strict application of the scoring rules is rank 4, or "somewhat greater than likely" to be MH. Eight experts ranked this scenario as 4; three experts ranked it as 5.

Results

Eleven MH experts created a MH clinical grading system that can be applied to two different situations: first, to estimate the qualitative likelihood that an adverse anesthetic event is clinical MH; and second, to estimate a subject's qualitative likelihood of MH susceptibility when the subject has a family history of MH susceptibility with or without personal experience of an adverse anesthetic event.

The qualitative likelihood that an adverse anesthetic event represents MH is based on points assigned to specific abnormal signs and laboratory findings (clinical indicators) observed during an acute anesthetic reaction. Points are assigned for each clinical indicator present; these points then are summed to produce a raw score that an adverse anesthetic reaction is a MH event. Additional clinical indicators for family history are added to the raw score to determine an individual's MH susceptibility. The raw score is designed to translate to a MH rank designating the risk with which MH could occur from 1 ("almost never") to 6 ("almost certain"). The MH rank should not be viewed as a percent likelihood; it is a qualitative indicator only.

Table 1 shows the scoring rules created by the MH experts for the MH clinical grading scale. The rules address the following issues. First, several agreed-upon indicators are manifestations of the same physiologic process. For example, increased end-tidal carbon dioxide tension to greater than 60 mmHg during spontaneous ventilation (15 points) *and* inappropriate tachypnea (10 points) each represent a sign of the same process: respiratory acidosis. Yet the experts believed that the MH score should not be the simple sum of all indicators present because it would overestimate likelihood, depending on how extensively the individual was monitored at the time of the possible MH event. Rather, only the single indicator with the highest point score within a given process would count toward the raw score. Therefore, in the example above, an individual who was inappropriately tachypneic with an end-tidal carbon dioxide tension of 70 mmHg during spontaneous ventilation would receive only 15 points for an end-tidal carbon dioxide tension greater than 60 mmHg and inappropriate tachypnea, and not 25 points, because both of these indicators are signs of the same respiratory acidosis process.

Second, because MH frequently is inherited as an autosomal dominant trait, it is important to ensure that adequate weight is given to a family history of MH (defined as a prior adverse metabolic or musculoskeletal reaction to anesthesia). Therefore, the following additional indicators were developed for use in determining an individual's MH susceptibility rank: positive MH family history in a relative of the first degree (15 points), positive MH family history in a relative not of the first degree (5 points), positive MH family history together with another indicator from the patient's own anesthetic experience other than elevated serum creatine kinase (10 points), and resting elevated serum creatine kinase in a patient with a family history of MH (10 points).

The clinical indicators used to determine the MH raw scores are listed in table 2. The precise wording of

Table 1. Scoring Rules for the Malignant Hyperthermia (MH) Clinical Grading Scale

MH indicators

Review the list of clinical indicators. If any indicator is present, add the points applicable for each indicator while observing the double-counting rule below, which applies to multiple indicators representing a single process.

If no indicator is present, the patient's MH score is zero.

Double-counting

If more than one indicator represents a single process, count only the indicator with the highest score. Application of this rule prevents double-counting when one clinical process has more than one clinical manifestation.

Exception: the score for any relevant indicators in the final category of table 2 ("other indicators") should be added to the total score without regard to double-counting.

MH susceptibility indicators

The italicized indicators listed below apply only to MH susceptibility. Do not use these indicators to score an MH event. To calculate the score for MH susceptibility, add the score of the italicized indicators below to the score for the highest ranking MH event.

Positive family history of MH in relative of first degree

Positive family history of MH in relative not of first degree

Resting elevated serum creatinine kinase

Positive family history of MH together with another indicator from the patient's own anesthetic experience other than elevated serum creatine kinase

Interpreting the raw score: MH rank and qualitative likelihood

Raw Score Range	MH Rank	Description of Likelihood
0	1	Almost never
3–9	2	Unlikely
10–19	3	Somewhat less than likely
20–34	4	Somewhat greater than likely
35–49	5	Very likely
50+	6	Almost certain

Table 2. Clinical Indicators for Use in Determing the Malignant Hyperthermia (MH) Raw Score

Process	Indicator	Points
Process I: Rigidity	Generalized muscular rigidity (in absence of shivering due to hypothermia, or during or immediately following emergence from inhalational general anesthesia)	15
	Masseter spasm shortly following succinylcholine administration	15
Process II: Muscle Breakdown	Elevated creatine kinase >20,000 IU after anesthetic that included succinylcholine	15
	Elevated creatine kinase >10,000 IU after anesthetic without succinylcholine	15
	Cola colored urine in perioperative period	10
	Myoglobin in urine >60 μg/L	5
	Myoglobin in serum >170 μg/L	5
	Blood/plasma/serum K^+ >6 mEq/L (in absence of renal failure)	3
Process III: Respiratory Acidosis	$P_{ET_{CO_2}}$ >55 mmHg with appropriately controlled ventilation	15
	Arterial Pa_{CO_2} >60 mmHg with appropriately controlled ventilation	15
	$P_{ET_{CO_2}}$ >60 mmHg with spontaneous ventilation	15
	Arterial Pa_{CO_2} >65 mmHg with spontaneous ventilation	15
	Inappropriate hypercarbia (in anesthesiologist's judgment)	15
	Inappropriate tachypnea	10
Process IV: Temperature Increase	Inappropriately rapid increase in temperature (in anesthesiologist's judgment)	15
	Inappropriately increased temperature >38.8°C (101.8°F) in the perioperative period (in anesthesiologist's judgment)	10
Process V: Cardiac Involvement	Inappropriate sinus tachycardia	3
	Ventricular tachycardia or ventricular fibrillation	3
Process VI: Family History (used to determine MH susceptibility only)	*Positive MH family history in relative of first degree**	15
	*Positive MH family history in relative not of first degree**	5
Other indicators that are not part of a single process†	Arterial base excess more negative than −8 mEq/L	10
	Arterial *p*H <7.25	10
	Rapid reversal of MH signs of metabolic and/or respiratory acidosis with iv dantrolene	5
	*Positive MH family history together with another indicator from the patient's own anesthetic experience other than elevated resting serum creatine kinase**	10
	Resting elevated serum creatine kinase (in patient with a family history of MH)*	10

* These indicators should be used only for determining MH susceptibility.

† These should be added without regard to double-counting.

each indicator, the point value assigned to each indicator, and the grouping of individual indicators into six separate processes are the result of the experts' voting during the Delphi process.

Qualitative ranks are the result of the expert consensual process, which determined how points should be grouped into an interval scale so that one can then qualitatively define the likelihood that an adverse anesthetic event represents MH and the individual's relative chance of being MH susceptible. In the calculation of the individual MH susceptibility rank, points accrued for positive family history should be added to those derived from the highest-ranking adverse anesthetic event.

Ranks for MH events and MH susceptibility were made separate because they may differ when a detailed investigation into an individual's family history reveals a family member with a history of a possible MH reaction that was unknown or unrevealed at the time of the initial anesthetic preoperative interview. Also, a separate rank for MH susceptibility permits the ranking of subjects with a positive family history who have never personally experienced an adverse anesthetic reaction.

Discussion

We used a consensual process among MH experts to construct a MH clinical grading scale because there is a pressing need for a clinical case definition and because no gold standard exists for diagnosing MH events or MH susceptibility. Gold standards do not exist for many medical syndromes, such as sudden infant death syndrome, eosinophilia–myalgia syndrome, and chronic fatigue syndrome. In response to the lack of a gold standard, researchers and clinicians in these fields have used consensus processes to develop clinical case definitions also.[16–18]

Many early signs of MH episodes present in a variable manner and may be confused with other medical conditions, such as insufficient anesthetic depth, hypoxia, hypercarbia, iatrogenic hyperthermia, heat stroke, sepsis, radiologic contrast material within the central nervous system, thyrotoxicosis, pheochromocytoma, and neurolept malignant syndrome.[4,19] Even patients who die from a MH event have no pathognomonic findings on autopsy using current techniques.[20] Discussion among MH researchers at annual conferences reveals the disparity of opinions and practices concerning the clinical definition of the MH syndrome. We propose the MH clinical grading scale presented in this report as a means for standardizing and qualitatively defining the decision process whereby experts and researchers use clinical information to diagnose MH. This research provides a new and comprehensive clinical case definition for the MH syndrome.

The MH clinical grading scale requires the anesthesiologist to judge whether specific clinical signs are appropriate for the patient's medical condition, anesthetic technique, and surgical procedure. If the anesthesiologist judges the clinical sign to be inappropriate, then it is counted as a MH clinical indicator. For 30% of the clinical indicators, we rely upon the judgment of the anesthesiologist caring for the patient at the time of the event because we feel that only he or she would have sufficient information to judge the many possible MH clinical signs. For example, the anesthesiologist must consider the appropriateness of hypercarbia, permitting this clinical sign to be evaluated within the context of various important factors, such as preexisting asthma or chronic obstructive pulmonary disease, anesthetic circuit type, fresh gas flow, quality of the airway, prior release of a surgical tourniquet, and use of cardiopulmonary bypass.

The anesthesiologist should accept the critical cutoff values given in the indicators unless unusual circumstances apply. Selection of some of the indicators listed in table 2 assumes that the anesthesiologist has evaluated and ruled out other more prevalent causes of the indicator or sign. For example, inappropriately increased temperature should not be counted in a patient's score if a coexisting active infection is believed to be the source of the fever; similarly, inappropriate sinus tachycardia should not be scored if the elevated heart rate can be attributed to the recent administration of an anticholinergic agent or an increase in the intensity of the surgical stimulus.

The assigned MH rank represents a lower bound on the likelihood of MH. Therefore, several factors including aborting an anesthetic at the beginning of a reaction may lead to an underestimation, but rarely an overestimation, of the likelihood of a MH event or an individual's MH susceptibility. For example, if triggering anesthetic agents are discontinued immediately after the development of masseter muscle rigidity and the patient develops no other clinical indicators of MH, then the patient's MH susceptibility will be ranked as "somewhat less than likely," whereas if triggering an-

esthetic agents were continued and the patient also developed inappropriate hypercarbia, arterial *p*H less than 7.25, arterial base excess more negative than −8 mEq/l, and an inappropriately rapid increase in temperature, then the patient's MH susceptibility would be ranked as "almost certain."

Also, the assigned MH rank may underestimate the likelihood of an MH event or MH susceptibility if important monitors (*e.g.,* electrocardiogram, capnometer, or temperature monitor) were not in use during the adverse anesthetic event or if relevant blood tests (*e.g.,* creatine kinase, serum and urine myoglobin, arterial blood gases, or potassium) were not obtained at appropriate times. While considered highly desirable, no consensus could be reached on a simple and practical way to differentiate between missing laboratory data (due to incomplete clinical investigation at the time of a possible MH event) and normal laboratory data. The MH susceptibility score might underestimate an individual's likelihood of MH susceptibility if the family anesthetic history cannot be obtained (*e.g.,* if the individual was adopted) or if family members have not been anesthetized with triggering agents. Above all, the scoring rules should be applied as an objective guide to the likelihood of a MH event and MH susceptibility, and there might be situations (*e.g.,* inability to obtain an arterial blood gas during cardiopulmonary resuscitation) in which incomplete data would produce a rank that underestimates the patient's MH susceptibility.

This grading system is intended to assist MH researchers in classifying adverse events that occur within 24 h of the administration of an anesthetic. The MH clinical grading system will be most useful to the researcher when it is used to rank and compare well monitored and well documented adverse anesthetic events.

At this time, the grading scale is not intended for use by the clinician. The physician should always give priority to the appropriate treatment rather than classification of the patient during a fulminant MH episode.††† Because patients with the rank of "somewhat less than likely" or even "unlikely" may still be susceptible to MH if they were incompletely monitored or evaluated during an adverse reaction to anesthesia, rank achieved on this clinical grading scale should not interfere with clinician referral of patients for further MH diagnostic evaluation.

The results of a caffeine halothane contracture test were intentionally not included in this grading scale because the determination of the sensitivity of any diagnostic test requires a prior clinical definition of the disease being tested. Thus, the sensitivity of the MH diagnostic muscle biopsy depends on a preexisting definition of MH; the test cannot, in itself, be used as a standard for diagnosing MH events or MH susceptibility.

As MacLennan recently emphasized, efforts to determine the specific molecular genetic and biochemical defects underlying MH susceptibility have been hindered by the absence of accurate phenotypic diagnosis.[12] Using this grading scale, we now anticipate that researchers can select human study subjects who are "almost certainly" MH susceptible as objectively determined by the MH clinical grading scale, without solely depending upon the caffeine halothane contracture test. This scale should be useful in the evaluation of new diagnostic laboratory tests of MH susceptibility, and in understanding the molecular mechanisms responsible for MH.

A Delphi process is only as strong as the knowledge, skills, and commitment of its participants. The result of our process, a set of rules for the definition of MH must be applied by researchers and updated to gain acceptance. Even without formal or universal acceptance, however, the process of achieving a consensus about the definition of a disease can generate serious dialogue, especially about improved standards for patient monitoring.

The importance of accurate and timely submission of reports of *all* patients having adverse metabolic or musculoskeletal responses to anesthesia to the North American MH Registry‡‡‡ or other national registries cannot be overemphasized. Such reports serve as the basis for accurate and standardized information concerning possible MH events for use in patient care and in research. Future studies will be required to refine scientifically this MH clinical grading scale. We view this MH clinical grading scale as an essential step in standardizing the analysis of adverse anesthetic events and improving prediction of MH susceptibility.

††† Gronert GA, Larach MG, Rosenberg H: Updated technical bulletin for malignant hyperthermia. American Society of Anesthesiologists Newsletter 56:30–31, 1992. A reprint may be obtained by writing to the American Society of Anesthesiologists, 515 Busse Highway, Park Ridge, Illinois 60068-3189.

‡‡‡ Confidential reporting forms can be obtained from the North American Malignant Hyperthermia Registry by writing to the first author or by telephoning 717-531-6936.

Appendix 1. Scoring* of Likelihood of Malignant Hyperthermia by 11 Experts and by Strict Application of Case Definition

Case Number	Expert											Case Definition Score†
	A	B	C	D	E	F	G	H	I	J	K	
1	4	4	5	4	4	4	5	4	5	4	4	4
2	4	3	4	3	4	4	4	3	4	3	4	3
3	6	6	5	5	5	6	5	5	5	4	4	6
4	6	6	5	5	6	6	6	6	6	6	6	6
5	2	1	2	1	1	2	3	2	3	1	2	2
6	4	4	4	3	3	3	3	3	5	3	4	4
7	4	4	1	2	3	3	3	3	4	3	2	3
8	6	5	6	6	5	5	4	4	5	2	5	6
9	1	1	1	2	1	1	1	1	3	1	1	1
10	2	1	2	2	1	1	1	2	3	1	1	1
11	1	1	1	1	1	2	1	1	2	1	1	1

* Possible scores range from 1 to 6 and indicate the likelihood of malignant hyperthermia: 1 = almost never; 2 = unlikely; 3 = somewhat less than likely; 4 = somewhat greater than likely; 5 = very likely; 6 = almost certain.

† Using strict application of malignant hyperthermia case definition (clinical grading score).

Appendix 2. Agreement among Experts on Likelihood of MH and Experts' Agreement with Strict Application of Case Definition*

Comparison	Level of Agreement
11 experts' independent judgment of 11 cases(95%) CI†	0.83 (0.75, 0.92)
Individual experts *versus* case definition score‡	
A	0.96 (0.91, 1.0)
B	0.96 (0.91, 1.0)
C	0.88 (0.77, 0.99)
D	0.90 (0.84, 0.96)
E	0.92 (0.86, 0.98)
F	0.94 (0.88, 0.99)
G	0.87 (0.75, 0.99)
H	0.89 (0.78, 1.0)
I	0.74 (0.61, 0.87)
J	0.70 (0.32, 1.0)
K	0.90 (0.79, 1.0)
Mean of 11 experts *versus* case score (95% CI)	0.88 (0.83, 0.93)

* Pairwise agreement of each expert individually with MH case definition score. Raw scores appear in appendix 1.

† Intraclass correlation coefficients were calculated using the SAS VARCOMP procedure[21] to measure agreement among the experts.[22] This statistical procedure assumes that experts are random effects, and thus it estimates agreement among any group of experts rather than among members of this particular panel. 95% confidence intervals were generated using the jackknife method.[23]

‡ Weighted Kappa statistics[24] measured pairwise agreement between the experts and a strict application of the scoring system as applied by one of us (M.G.L.). 95% confidence intervals were computed using variance estimates under the alternative hypothesis of agreement greater than chance.

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