CLINICAL DIAGNOSIS AND ASSESSMENT OF SEVERITY OF CONFIRMED DENGUE INFECTIONS IN VIETNAMESE CHILDREN: IS THE WORLD HEALTH ORGANIZATION CLASSIFICATION SYSTEM HELPFUL?

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Abstract. Classification of dengue using the current World Health Organization (WHO) system is not straightforward. In a large prospective study of pediatric dengue, no clinical or basic laboratory parameters clearly differentiated between children with and without dengue, although petechiae and hepatomegaly were independently associated with the diagnosis. Among the 712 dengue-infected children there was considerable overlap in the major clinical features. Mucosal bleeding was observed with equal frequency in those with dengue fever and dengue hemorrhagic fever (DHF), and petechiae, thrombocytopenia, and the tourniquet test differentiated poorly between the two diagnostic categories. Fifty-seven (18%) of 310 with shock did not fulfill all four criteria considered necessary for a diagnosis of DHF by the WHO, but use of the WHO provisional classification scheme resulted in considerable over-inflation of the DHF figures. If two separate entities truly exist rather than a continuous spectrum of disease, it is essential that some measure of capillary leak is included in any classification system, with less emphasis on bleeding and a specific platelet count.

INTRODUCTION

Infection with dengue virus, which is endemic in many parts of Asia and the Americas, is increasingly being recognized as a major public health issue in the tropical world.1,2 Currently, approximately 2.5 billion people live in areas of risk and it is expected that this number will increase as transmission spreads to neighboring geographic regions.3,4 In endemic areas, symptomatic dengue infection is one of the leading causes of hospitalization and death among children.5 Each year an estimated 100 million cases of dengue fever (DF) occur, and between 250,000 and 500,000 cases of dengue hemorrhagic fever (DHF) are reported to the World Health Organization (WHO).3,6

As a result of the progressive increase in the number and severity of cases over the last 40 years, attempts have been made to describe and categorize the common manifestations of dengue, and to develop simple and universally applicable algorithms for diagnosis and management. Pioneering studies in Thailand in the 1950s and 1960s established the common patterns of disease at that time,7−9 and from that body of work the current WHO classification system has evolved.10,11 This system differentiates between DF, a non-specific febrile illness with prominent constitutional symptoms sometimes accompanied by bleeding manifestations, and DHF, in which increased vascular permeability leads to capillary leak syndrome that may, in the most severe cases, progress to dengue shock syndrome (DSS). According to the WHO, increased vascular permeability is always accompanied by some form of hemorrhagic manifestation, thus the term dengue hemorrhagic fever.

One important aim of the WHO classification system is to allow prompt identification of those patients most at risk of developing severe dengue-related complications from among the large number of children presenting to health care facilities in endemic areas, and thus to facilitate triage and appropriate use of scarce resources. Second, it is intended that the system be used as an epidemiologic tool to collect public health data on incidence of symptomatic infection, disease severity, etc., which can then be compared between different geographic locations or over time. For any classification system to be useful, it must be simple and reproducible, use readily available information, and should be applicable to the majority of cases without modification or interpretation. Unfortunately, since there is considerable overlap in both the clinical and laboratory features of DF and DHF, classification of dengue cases is often difficult, and in the absence of an independent diagnostic marker, no validation of the WHO system has yet been attempted. In recent years, several large descriptive studies of the clinical manifestations of dengue infection have been published, but most have been retrospective series describing patients attending multiple facilities.12−15 While such studies may provide useful information on dengue infection in general, the necessary detail for formal disease classification is often lacking, and interpretation of the significance of the clinical information is limited without a contemporary comparison group of children with febrile non-dengue illnesses. In one detailed prospective study from Thailand involving 60 patients and including a comparison group, difficulties with classification were encountered in approximately 20% of the children.16 Other investigators have reported inconsistencies in the WHO classification system,17 and some have found it necessary to define new categories to reflect the patterns of disease identified more accurately.18−20

The purpose of this study was to attempt to describe systematically the spectrum of clinical dengue in a large number of children presenting to a single institution in Vietnam, and to identify any factors associated with the development of shock or bleeding, the two major complications of infection. By choosing broad entry criteria, we hoped to include not only those with DF, DHF, and DSS, but also a comparison group of children with other non-dengue febrile illnesses. Second, we wished to evaluate the usefulness of the WHO classification system when applied in the context of a busy pediatric practice in a dengue-endemic area. In the absence of an independent gold standard to assess the accuracy of DF/DHF

* Deceased.
diagnosis, we elected to use the presence of shock in dengue-infected children as a marker of DHF, since shock should only occur in those with DHF and the cardiovascular criteria that must be fulfilled for a diagnosis of shock are clearly defined and specific.

METHODS

Patients and clinical methods The study took place at the Dong Nai Pediatric Center (DNPC), the main health care provider for children in Dong Nai Province in southern Vietnam. Previously healthy children presenting directly to the facility with clinically suspected dengue of any severity were eligible for inclusion in the study provided a parent or guardian gave informed consent. The hospital’s guidelines for suspecting dengue include any child with a febrile illness lasting less than seven days, with a negative malaria smear, and without clinical signs suggesting an alternative diagnosis (e.g., pneumonia, meningitis, etc).

Up to five children a day were enrolled and admitted to either the infectious disease ward or the intensive care unit, depending on severity. History and detailed examination findings, including a tourniquet test, were recorded on standard proforma shortly after admission. An admission serum sample was frozen and stored for subsequent flavivirus serology, in conjunction with a second sample obtained at discharge. Hematocrit estimations and manual platelet counts were performed on admission and at intervals during the hospital stay depending on the clinical course, together with any other investigations deemed appropriate by the clinicians. Children were assessed daily by a member of the study team, and at discharge a summary of the clinical course was completed, focusing particularly on the occurrence of hemorrhagic manifestations and the development of shock. The WHO criteria for diagnosis of shock were used, namely either a pulse pressure ≤20 mm of Hg, or hypotension for age (systolic blood pressure <80 mm of Hg if <5 years old or <90 mm of Hg if ≥5 years old).

During the study period an intervention trial took place that involved 230 of the children with DSS, in which the efficacy of various crystalloid and colloid solutions for emergency resuscitation was evaluated. The details of this trial have been published elsewhere.

The remaining children with DSS were resuscitated in a standardized manner similar to the trial protocol, using 20 mL/kg of Ringer’s lactate given over the first hour for primary resuscitation, with 6% dextan 70 for rescue treatment. For each patient with shock, the number of hours taken to achieve cardiovascular stability (defined as a pulse pressure consistently ≥25 mm of Hg), the overall parenteral fluid requirement, and any requirement for rescue colloid therapy were noted.

Ethical review. Ethical approval and scientific review were obtained from the Scientific and Ethical Committees of the Dong Nai Pediatric Centre and the Hospital for Tropical Diseases of Ho Chi Minh City. Informed consent was obtained from the parents or guardians of the patients.

Serologic/virologic studies Paired serum samples were tested for serologic evidence of acute dengue infection by capture enzyme-linked immunosorbent assay (ELISA) for dengue and Japanese encephalitis viruses in one of two laboratories, either the Institute of Health and Community Medicine in Sarawak, Malaysia or the Department of Virology at the Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand. Criteria for serodiagnosis were as described previously for each laboratory.

For some patients, a definitive serodiagnosis was not possible either because no convalescent sample was obtained or because the interval between the two serologic samples was insufficient. In the Malaysian laboratory, virus isolation and serotype identification was attempted by inoculation of C6/36 mosquito cell lines, followed by a reverse transcriptase–polymerase chain reaction on all isolates using the primers of Taneka and others, and also by using an in-house antigen capture ELISA on all negative cultures.

Final diagnosis and disease classification. Patients with serologic evidence of acute dengue infection, and/or from whom a dengue virus was isolated, were considered to have confirmed dengue; those with definite negative serology and/or a well-substantiated alternative diagnosis were categorized as not dengue (ND); finally, in the absence of a well-substantiated alternative clinical diagnosis, children with inconclusive serology were classified as indeterminate. After discharge patients with confirmed dengue were further classified as having either DF or DHF using all available clinical and laboratory data, according to the criteria indicated in Table 1, based on the WHO criteria for dengue classification.

These criteria stipulate that plasma leakage can be inferred from a peak hematocrit ≥20% above the mean for the population. From a simultaneous study at the DNPC involving more than 1,000 medical admissions, the mean hematocrit in children between 5 and 10 years of age, the common age range for DHF, was 37% (CXT Phuong, unpublished data), thus giving a cut-off value for hematocrit evidence of plasma leakage for this study of 44%. Patients who did not fulfill all the criteria for DHF but had serologic

<table>
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<th>Table 1</th>
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<tr>
<td>Criteria used for the diagnosis of dengue fever and dengue haemorrhagic fever, adapted from the World Health Organization guidelines (patients must satisfy all the criteria stipulated for the respective diagnoses)</td>
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<td><strong>Basic clinical features</strong></td>
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<tr>
<td><strong>Dengue fever</strong></td>
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<td><strong>Dengue hemorrhagic fever</strong></td>
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* e.g., skin petechiae, bruising, mucosal/gastrointestinal bleeding.
† The mean hematocrit for children 5–10 years old hospitalized with any medical diagnosis at Dong Nai Pediatric Hospital in 37% (see text). We have chosen a cut-off value ≥44% as evidence of increased vascular permeability, this value being approximately 20% above the mean for the population.
or virologic evidence of dengue infection were classified as having DF, provided all the information necessary for classification was available.

**Statistical analysis.** Patient data and laboratory results were compared between the various diagnostic groups using the chi-square test or Fisher’s exact test for categorical variables, and the Mann-Whitney or Kruskal-Wallis tests for continuous variables. For those patients with a definitive serologic diagnosis either confirming or refuting dengue infection, variables significant in the univariate analysis were subsequently entered in a logistic regression model to identify independent associations. The final model was constructed using a forward stepwise variable selection procedure. Among those treated for shock, three outcome indicators were examined: the time taken to achieve cardiovascular stability, the total volume of parenteral fluid administered, and the volume of any rescue colloid therapy required. For determination of factors influencing these indicators, the Kruskal-Wallis test was used for categorical variables and Spearman’s correlation was used for continuous variables. All statistical computations were carried out using STATA 5 (Stata Corp., College Station, TX).

**RESULTS**

Between June 1996 and June 1998, 1,136 children with suspected dengue infection were admitted to the DNPC and enrolled in the study. Of this group, 396 (35%) had clinical DSS, with the remainder manifesting less severe disease patterns. No patient in the study group died. Among the 1,136 study patients, 712 were confirmed to have acute dengue infections, with 85 categorized as definitely not dengue and 339 as indeterminate (Figure 1). Of the 712 children with confirmed dengue, 312 (44%) were classified as having DF and 319 (45%) as having DHF. Essential information was missing in the remaining 81 children, which precluded classification.

In the group without dengue, six children had confirmed typhoid fever, one had *P. falciparum* malaria, and one developed a measles-like rash with transient cardiovascular compromise that required a single bolus of intravenous fluid for resuscitation. Dengue serology was negative for this patient. The remainder of the ND group had no specific alternative diagnosis but serology was convincingly negative; most are likely to have had other viral infections.

Serologic responses could be defined as primary or secondary in 327 patients. In 35 (11%) the response was primary; all these children were classified as having DF, and none developed shock. The remaining 292 children had secondary antibody responses, 116 (40%) with DF, 174 (60%) with DHF, and the remaining 2 children lacking information for disease classification. A virus was isolated from 77 children, 90% of whom presented before the fourth day of illness; dengue 1 in 2 cases, dengue 2 in 34 cases, dengue 3 in 38 cases, dengue 4 in 1 case, and mixed infections with dengue 2 and 3 in the remaining 2 cases. There were no associations between the serotype isolated and disease classification.

**Comparison of confirmed dengue and not dengue groups.** Children with dengue were significantly older, presented later in the course of their illness, and had less respiratory but more gastrointestinal symptoms than those in the ND group (Table 2). Anorexia, vomiting, and abdominal pain occurred in more than 60% of the dengue-infected group but were also noted in 35–48% of the ND group. Headache, muscle pain, and joint pain were no more common in the dengue group than in the ND group. Mucosal bleeding, mainly epistaxis or gum bleeding, was reported in 15% of the dengue group, compared with 11% of the ND group. However, spontaneous petechiae were noted in twice as many of the dengue patients, and the tourniquet test result was positive in 42% of this group, compared with only 5% of the ND group (relative risk = 12.84, 95% confidence interval [CI] = 4.69–48.96, *P* < 0.01). Significant liver enlargement was much more frequent in the dengue patients. There was a slight but significant difference between the two groups in admission hematocrit, with children with dengue having higher values. Moderate thrombocytopenia was very common in both groups, with 81% of the dengue group and 65% of the ND group having platelet counts ≤ 100,000/mm³ on admission. However, the absolute values were significantly lower in the dengue group.

Logistic regression (Table 3) demonstrated that both skin petechiae and hepatomegaly were independently associated with confirmed dengue, while sore throat and cough were associated with not having dengue infection. Children pre-

![Figure 1](image-url)  
**Figure 1.** Schematic diagram showing the final disease classification for all children enrolled in the study.
senting after more than three days of illness were more than twice as likely to have dengue infection, compared with those presenting earlier. Higher hematocrit values were also associated with confirmed dengue infection. However, there was a statistically significant interaction between hematocrit and the day of presentation, and further analysis showed that the association between an increased hematocrit and dengue infection was only apparent in children presenting after day three of illness (odds ratio = 1.25, 95% CI = 1.13–1.40, \( P < 0.01 \)).

**Comparison of the DF and DHF groups.** Admission signs, symptoms, and laboratory investigations that demonstrated significant differences between patients classified as having either DF or DHF are shown in Table 4. Age and sex profiles were similar for the two groups. Children with DHF presented later in the course of their illness, with prominent gastrointestinal symptoms and more hepatic enlargement. However, headache and lymphadenopathy were more frequently noted in children with DF. Mucosal bleeding was also reported more often by children with DF than those with DHF, but petechiae were more frequent in those with DHF, although common in both groups. Detailed results of the tourniquet test findings have been reported elsewhere.26 Briefly, a positive tourniquet test result, while statistically more common in the DHF group, differentiated poorly between DF (39% positive) and DHF (47% positive). Admission hematocrit was higher and platelet count was lower in the children with DHF.

**Clinical features affecting outcome.** Shock and bleeding are the two important complications of dengue infection. Among the 712 children with confirmed dengue, 255 (36%) were shocked at presentation, a further 86 (12%) went on to develop shock during the hospital admission, and the remaining 371 children were never shocked. Children who experienced shock were slightly younger than those without shock, with the median (90% range) age being 7 (3.5–13) years in those with shock and 8 (3.8–14) years in those who did not develop shock (\( P = 0.03 \)). Significantly more girls required treatment for DSS (179 [53%] of 338) compared with boys (162 [43%] of 374) (\( P = 0.01 \)). Among those with established DSS who received 20 mL/kg of fluid for initial resuscitation, early shock was associated with a significantly poorer outcome in terms of time to cardiovascular stability and requirement for parenteral fluids (Figure 2).

**Table 3**

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<th>Independent variable</th>
<th>Odds ratio (95% confidence interval)</th>
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<tr>
<td>Petechiae</td>
<td>4.82 (2.71–8.58)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hepatomegaly ( \geq 1 ) cm</td>
<td>2.93 (1.14–7.53)</td>
<td>0.03</td>
</tr>
<tr>
<td>Admission after day 3 of illness</td>
<td>2.47 (1.38–4.42)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>1.13 (1.05–1.22)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Coryza</td>
<td>0.36 (0.16–0.81)</td>
<td>0.01</td>
</tr>
<tr>
<td>Sore throat</td>
<td>0.33 (0.14–0.76)</td>
<td>&lt;0.01</td>
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come measures in this study, although both are thought to be indirect measures of the severity of illness. It is likely that the percentage increase in hematocrit would represent the severity of capillary leak more accurately, but in the absence of premorbid hematocrit data we were unable to investigate this possibility. However, a peak hematocrit of 50% or more was associated with significantly worse outcomes ($P < 0.03$ for all three outcome indicators).

Although reported bleeding at presentation was more frequent in those with DF than in those with DHF, there was no difference in mucosal bleeding observed in the hospital between the two groups. However it was more common in those with shock, with 97 (28%) of 341 children treated for DSS (includes children classified with DF and DHF) developing some form of mucosal bleeding compared with 64 (17%) of 371 children without shock ($P < 0.001$). In virtually all cases the bleeding was minor, and only one child required a transfusion. The development of bleeding was not associated with a positive tourniquet test result, or with admission/maximum hematocrit or admission/minimum platelet values.

**World Health Organization classification.** Of the 310 shocked children with confirmed dengue and all necessary information available to allow formal classification, 57 (18%) failed to meet the four criteria necessary for a diagnosis of DHF, and were thus classified as having DF by default (Figure 3); 22 failed because they had a negative tourniquet test result and no bleeding manifestations throughout the hospital stay, 15 because the platelet count was never less than 100,000/mm$^3$ (range = 102,000–162,000/mm$^3$), and the remaining 20 because they did not reach the predefined hematocrit cut-off value of $\geq 44\%$ (range = 38–43%). The WHO guidelines allow for a modification of the classification system whereby a diagnosis of DHF can be made if two of the criteria (fever and some evidence of bleeding) are met, together with either of the two remaining criteria (hemoconcentration or thrombocytopenia). The sensitivity and specificity of this and other possible modifications to the classification system are shown in Table 5. The WHO modified system correctly identified 93% of those with shock, but in addition reclassified 168 (66%) of the DF patients without shock as having DHF. The classification system of fever and hemoconcentration with either bleeding or thrombocytopenia identified 94% of the shocked children correctly, with only an extra 15 DF cases without shock.

**DISCUSSION**

We present the results of a large prospective descriptive study of pediatric dengue conducted in a single institution. All children enrolled in the study were initially suspected to have dengue, but 85 (11%) of the 797 children with a definitive diagnosis proved to be seronegative, allowing comparisons between those with dengue and those with similar non-dengue febrile illnesses. In general agreement with others, we found that children with dengue were significantly older and had more gastrointestinal symptoms than those without dengue. However, it was difficult to identify characteristics that distinguished clearly between the two diagnostic groups since so many of the features were common to both groups. In the non-dengue group respiratory symptoms were prominent, consistent with the prevalence of respiratory infections in childhood. More children with dengue presented after the third day suggesting that, fever aside, in the early stages of infection these children are less symptomatic than those with non-dengue febrile illnesses. Musculoskeletal symptoms, often reported by adults with dengue, occurred infrequently, confirming the view that children with uncomplicated dengue infections are less symptomatic than adults. The main features associated with DHF were skin petechiae, hepatomegaly, and gastrointestinal symptoms. Dengue shock syndrome occurred significantly more frequently in girls than boys, and the children with shock tended to be slightly younger. A predisposition towards shock among girls has been noted previously, and epidemiologic studies indicate that mortality is higher in younger children with dengue. Research on microvascular permeability suggests that even in health perme-
ability is influenced by age and sex, with the greatest filtration capacity being documented in the youngest age groups.****

Fever, bleeding, thrombocytopenia, and increased vascular permeability are said to be the hallmarks of DHF. However, we noted similarly low rates of mucosal bleeding in the dengue and ND groups, with a slightly higher rate in the DF patients compared with the DHF patients. Overall, the findings were similar to those in a recent study from Thailand,16 although reports from India18 and the Philippines12 do suggest that bleeding manifestations may be more common in dengue-infected patients in other geographic regions. Petechiae occurred more frequently in the children with DHF, but as with the tourniquet test, discriminated poorly between DF, DHF, and non-dengue febrile illnesses. Thrombocytopenia, probably one of the major determinants of both skin and mucosal bleeding, was extremely common in all groups and also failed to differentiate clearly between DF, DHF, and other febrile illnesses. Moderate thrombocytopenia is associated with many of the common virus infections of childhood, and the finding of ≤100,000 platelets/mm$^3$ is neither specific to DHF nor essential for the diagnosis.

Identification of increased vascular permeability without shock is often difficult. Clinical detection of pleural effusions or ascites is not reliable unless the volumes of fluid are large. In addition, ultrasound facilities are commonly only available in larger hospitals in the tropics, and repeated X-rays expose the patient to unnecessary radiation. Documentation of hemoconcentration by serial hematocrit estimations, although not without problems, is the most readily available surrogate measure of capillary leak. In this study, by using a local population mean hematocrit as a baseline and adopting the WHO recommendation of a 20% increase above this value, we correctly identified 94% of the shocked patients as having capillary leak. Use of a population mean value thus proved to be an effective tool, although it must be appreciated that whatever cut-off value is chosen some patients with true shock...
capillary leak will not achieve this degree of hemoconcentration even when shocked. Notwithstanding the expected variability in baseline hematocrits, we have shown that a hematocrit value ≥50% in children is almost invariably associated with shock.

Thus, of the four criteria recommended by the WHO to indicate a diagnosis of DHF, two (bleeding and thrombocytopenia) occurred almost as frequently in the children with DF as in those with DHF, and were also relatively common in children with other febrile illnesses. Clinical shock requiring fluid resuscitation is one independent marker that strongly implies that a child has DHF, although it only identifies the severe end of the spectrum. However, we found that 18% of the children with DSS failed to meet all four of the necessary criteria for DHF. Therefore, not only are bleeding and thrombocytopenia common in children without apparent DHF, but these features are also absent in some children with “true” DHF.

Overall, however, 82% of the children with shock were identified correctly by the strict WHO classification system. In some circumstances, for example for recruitment to a trial of a specific intervention for DHF, it may be desirable for a disease classification system to be very specific at the expense of sensitivity. Among the 85 definitely seronegative children, only three would have met all the criteria for a diagnosis of DHF, and had we chosen a hematocrit cut-off value >45%, none would have been classified as having DHF. However, in clinical practice many physicians use the modified WHO criteria of fever and bleeding, usually together with thrombocytopenia rather than hemoconcentration. In our study, while this modification did identify 93% of the children with shock, it also resulted in a large increase in the number of children with probable DF reclassified as DHF, leading to considerable inflation of the DHF figures. For individual patients, this simply leads to more careful observation, but in countries with limited resources it may result in intolerable pressure on an already overburdened health care system especially during epidemics. Second, epidemiologic data generated from disease notifications to the WHO become meaningless; valid mortality and morbidity comparisons are only possible when disease definitions are understood and applied in a uniform manner by all groups involved. If a modified classification system is to be recommended by the WHO, it ought to identify most of the patients with shock as cases of DHF, with the minimum increase in the number of probable DF cases classified as DHF. The classification system of fever and hemoconcentration, together with either bleeding or thrombocytopenia, approximates most closely this ideal. We suggest that this merits further evaluation in large prospective series from other dengue-endemic regions and might be preferable to the current WHO provisional classification scheme.

The study also raises the larger question of whether DF and DHF are truly two separate entities or are instead part of a continuous spectrum of dengue disease. Current thinking implies that bleeding and thrombocytopenia are reliable indicators of, or prerequisites for, the subsequent development of the shock syndrome, and that these clinical features are linked to one other by some as yet unidentified mechanism unique to DHF. These data suggest that this is not the case. The clinical manifestations show considerable overlap (Figure 3), and the data are more in keeping with a paradigm in which dengue virus infection disrupts a number of different physiologic systems to varying degrees in individual patients and the relative prominence of the resulting abnormalities determines the clinical picture. Many factors including differences in virus burden, intrinsic viral virulence, the host immune response, immune enhancement etc. are likely to contribute to the final disease expression. Research to try to understand the pathophysiologic mechanisms underlying the various clinical manifestations seen in dengue infections is urgently needed, and should help to determine whether truly separate disease entities exist.

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