Vascular Depression: A Distinct Diagnostic Subtype?

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Vascular depression has been proposed as a unique and valid diagnostic subtype on the basis of studies of external (concurrent and predictive) validity. Validating a diagnostic entity on the basis of external validity is problematic, because it presupposes that the construct is well defined (i.e., the proposed features cluster together to define a distinct patient group). Because such evidence has not been obtained, we propose that the next critical step in evaluating this potential subtype is to establish internal (construct) validity and highlight taxometric analysis and latent class cluster analysis as illustrative multivariate statistical techniques that can be used in this effort. The psychometric approach advocated here (despite its inherent assumptions and limitations) might substantially improve on previous diagnostic efforts (e.g., expert consensus), and vascular depression might serve as a prototype for future psychiatric classification.

Key Words: Vascular depression, late-onset depression, MRI hyperintensities, executive dysfunction, psychiatric nosology, diagnostic validity

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association 1994), criteria for major depressive disorder (MDD) do not vary across the adult age span. Instead, diagnostic criteria are expected to apply to older adults in the same way they apply to younger adults. However, this ignores the physical, psychological, and social role changes that are associated with aging and that might influence the course and presentation of depression. For example, older adults tend to report less depressed mood and more somatic symptoms than younger adults (Gallo and Rabins 1999). Such findings raise an important question: Are there subtypes of MDD that are distinct to old age?

One subtype that might be specific to older adults is vascular MDD (Alexopoulos et al 1997a; Hickie et al 1995; Krishnan and McDonald 1995; Steffens and Krishnan 1998). The notion of vascular MDD initially emerged from the finding that patients with late-onset MDD had higher rates of encephalomalacia or hyperintensities (HIs) on structural magnetic resonance imaging (MRI) compared to patients with early-onset MDD (Hickie et al 1995; Krishnan et al 1997; Salloway et al 1996). It was further observed that patients with late-onset depression and MRI evidence of cerebrovascular disease also demonstrated greater neuropsychological (NP) impairment, including but not limited to deficits in executive function (Alexopoulos et al 1997b; Lesser et al 1996; Salloway et al 1996). On the basis of these observations, it was hypothesized that some late-onset MDD occurs as a consequence of structural brain damage secondary to ischemia that creates a vulnerability to MDD precipitated by psychosocial risk factors such as negative life events or lack of social support (Krishnan and McDonald 1995).

Much about the vascular depression hypothesis is compelling. There is an established relationship between vascular disease and MDD. The best example of this is the relationship between acute cerebrovascular accidents (CVA) and the development of depression; the rate of MDD after acute CVA is approximately 20% (Robinson 2004). Whereas there is ongoing debate about the location of lesions in post-stroke MDD patients, there is some suggestion of an over-representation in the left frontal lobe and basal ganglia after acute cerebrovascular accident (CVA) (Robinson 2004). Indeed, MDD seems to be a more common consequence of basal ganglia compared with thalamic stroke (Starkstein et al 1988), and rates of HI in the basal ganglia have approached 50% in some late-life depression samples compared with 5% or less in healthy comparison samples (Coffey et al 1990). The deep white matter hyperintensities (DWMH) seen in late-onset depressed older adults might also be over-represented in anterior brain areas (Greewald et al 1998) and are thought to invade frontal-subcortical circuits that reciprocally link prefrontal areas such as the dorsolateral prefrontal cortex to the basal ganglia (Alexopoulos 2001; Alexopoulos et al 1997b; Thomas et al 2002, 2003), areas that are critical to mood regulation and executive functioning. Thus, the distal effect of HIs in disrupting corticostriatal circuits provides the necessary conditions for the emergence of vascular MDD.

Diagnostic Criteria for Vascular MDD

Proponents of the vascular MDD subtype have proposed different diagnostic criteria for the illness. Alexopoulos et al (1997a) regarded clinical and/or laboratory evidence of vascular disease and depression onset after age 65 as cardinal features and NP impairment as a secondary feature. Steffens and Krishnan (1998) regarded clinical and/or neuroimaging evidence of cerebrovascular disease or NP impairment as the cardinal features and age-of-onset > 50 as an additional supporting feature. Krishnan et al (2004) have further refined the notion of vascular MDD, requiring only MRI evidence of cerebrovascular pathology to define it and have referred to this syndrome as subcortical ischemic depression (SID). Alexopoulos has also refined the notion of vascular MDD. He has proposed a depression executive dysfunction (DED) disorder of late-life that, although recognizing the role of cerebrovascular pathology in the etiology of the illness, only requires executive dysfunction to meet diagnostic criteria (Alexopoulos 2001; Alexopoulos et al 2002). Although the proposed criteria sets are important and have moved the field toward recognizing a potentially important subtype of late-life MDD, this recognition might be premature because there is no agreement on how the construct is defined.

External Validity of Vascular MDD

Researchers have suggested that vascular MDD meets criteria for a valid diagnostic subtype on the basis of external (concurrent

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and predictive) validity (Krishnan et al 2004; Steffens and Krishnan 1998). However, basing the diagnostic validity of vascular MDD on evidence of external validity is problematic because it presupposes that the construct is well-defined (i.e., a homogeneous group of patients exist with features corresponding to the diagnosis in question). In fact, relying on studies of external validity reveals two levels of problems: 1) there is no consensus regarding how the subtype is defined so it is unclear how to interpret conflicting findings; and 2) even if there were consensus, there is considerable variability in the way the defining criteria are operationalized.

The problem with relying on external validators in the absence of agreement about the criteria used to define the illness is that there is no way of knowing what subtype is being externally validated. For example, Alexopoulos et al (2002) used the initiation/preservation domain of the Dementia Rating Scale to classify patients with and without DED and found that patients with DED showed greater impairment on instrumental activities of daily living and no difference in family history of mental illness as compared with non-DED patients. In contrast, Krishnan et al (2004) used hyperintensity load to classify patients with and without SID and found that patients with SID had a more negative family history of mental illness and no difference on instrumental activities of daily living as compared with non-SID patients. These studies used different definitions to define their patient groups. Because we do not know to what degree these two presumably different patient groups overlap, there is no way to evaluate the discrepant findings. For example, do they overlap to the point that they identify the same patient group or do they represent two unique, non-overlapping, subtypes? Studies of external validity cannot resolve this issue.

Not only is there no consensus about what defines the illness but the definition of each proposed feature is measurement-dependent at every level of the vascular MDD hypothesis. Alexopoulos et al (1997b) compared the symptom profile of patients with and without vascular MDD and found that the vascular MDD group scored significantly higher on psychomotor retardation and lack of insight. Evidence of vascular disease was defined in this study as a vascular score of 1 or more on the Cumulative Illness Rating Scale–Geriatrics (CIRS-G). Krishnan et al (1997) also compared the symptom profile of patients with and without vascular MDD (n = 37) and found no differences with respect to loss of interest, psychomotor retardation, or guilt feelings. Evidence of vascular disease was defined in this study as having a score of 2 or more on either deep white matter or subcortical gray matter hyperintensity ratings on MRI. Although in these two studies both Alexopoulos and Krishnan required evidence of vascular disease for a patient to be classified as having vascular MDD, they used different operational definitions. In fact, it is not at all clear what the relationship is between the CIRS-G total score or its vascular subscore and MRI-hyperintensity load. In fact, in one study, the two measures were unrelated (Krishnan et al 2004).

The difficulty with researcher-based definitions of vascular MDD is especially evident when it comes to determining what constitutes the age cutoff for late-onset MDD. Some researchers use an age cutoff of 50 years (Baldwin et al 2004; Hickie et al 1995; Lesser et al 1996; Steffens and Krishnan 1998), whereas others use an age cutoff of 60 years (Alexopoulos et al 1997b; Salloway et al 1996). Devanand et al (2004) recommended using an age cutoff of 60 years because differences in cardiovascular risk factors and family history of affective illness were strongest between the early- and late-onset depressed groups with this cutoff. In contrast, Krishnan et al (1995) recommended using an age cutoff of 50 years, citing genetic studies showing that familial effects are decreased and structural changes more common after this age. Krishnan et al (1997) variously defined late-onset as MDD occurring for the first time after ages 40, 45, and 50 years and detected statistically significant effects for age 40 but not for ages 45 or 50. Finally, Alexopoulos et al (1997a) proposed that age-of-onset > 65 years (or a significant change in the course of MDD) should be considered a cardinal feature of vascular MDD.

Although the underlying notion of late age-of-onset might be true, there might be psychometric problems inherent in assessing age-of-onset accurately. For example, as Krishnan et al (2004) suggested, defining late age-of-onset is difficult; should we consider it to be first symptoms of depression or onset of a defined syndrome? Retrospective reporting bias only complicates the issue. For example, a patient's recall of past affective episodes might not provide sufficient data to distinguish between intermittent, chronic, and perhaps subthreshold depressive symptomatology and first onset of major depression. Thus, it is possible that age of onset will be of limited utility as a diagnostic criterion. Despite these limitations, it is also possible that late age-of-onset simply does not contribute meaningfully to the identification of the illness. For example, it is conceivable that a young patient with cerebrovascular disease secondary to hyperlipidemia might develop a "vascular depression."

Internal Validity of Vascular MDD

At this point, we do not know whether the different criteria sets that have been proposed are simply variations of a single underlying entity or whether they define distinct patient groups (e.g., what is the diagnostic overlap, if any, between DED and SID). We do not know what features best define vascular MDD, the extent to which each feature contributes unique variance to the diagnosis, and whether these features actually cluster together to define a distinct diagnostic group. Thus, the first step in a programmatic line of structural research is to determine the internal (construct) validity of vascular MDD. By internal (construct) validity we mean that the specified clinical features associated with vascular MDD are jointly indicative of the underlying diagnostic classification (Young et al 1986). In other words, in the absence of a gold standard, each of the presumed defining features of the illness must be shown to be related to the latent construct representative of the proposed diagnostic group. Establishing such internal validity is integral to a categorical approach to psychiatric classification. According to the DSM-IV (American Psychiatric Association 1994), "A categorical approach to classification works best when all members of a diagnostic class are homogeneous, when there are clear boundaries between classes, and when the different classes are mutually exclusive" (p. xxii).

To date, research has documented important associations between late age-of onset, MRI hyperintensities, and cognitive impairment; however, the divergent diagnostic criteria that have been proposed as a result of these observations are hypotheses in need of testing and not validated diagnostic criteria. Indeed, as Kendler (1990) points out, the initial step in establishing a scientific nosology is to form empirically testable hypotheses in the form of competing diagnostic criteria. Consequently, the next critical step in the evolution of the vascular MDD subtype is to evaluate internal (construct) validity.

Statistical Approaches to Evaluating Internal (Construct) Validity

A number of alternative multivariate statistical approaches exist to evaluate the internal (construct) validity of psychiatric diagnoses, in general, and vascular MDD, in particular. One major advantage of statistical approaches to diagnostic classification as opposed to researcher-based classification is that researcher assignment ignores error (assumes classification is perfect), whereas error is inherent in statistical modeling and therefore more accurately represents the process of diagnosis. Latent class cluster analysis and taxometric analysis represent two alternative statistical approaches that can aid in developing a scientific nosology of psychiatric disorders.

Latent class cluster analysis (LCCA) is based on the assumption that the observed (manifest) indicators are imperfect measures of an underlying (latent) class (e.g., vascular or nonvascular MDD). A latent class model attempts to explain the association among several manifest indicators by virtue of their common association with this underlying, latent class. The fundamental assumption of LCCA is that individuals belonging to a particular latent class cannot be distinguished from each other on the basis of their observed response pattern on the manifest indicators. This is known as local independence.

Latent class cluster analysis produces two sets of probabilities: conditional and unconditional. The unconditional probabilities provide information regarding the likelihood that a person is in a particular class, whereas conditional probabilities allow the researcher to interpret the meaning of the classes; that is, they represent the likelihood that an individual belonging to a class will score a certain way on a set of manifest variables (Rindskopf and Rindskopf 1986). Of course, the researcher is more interested in finding the probabilities of latent class membership given a particular response set on the manifest indicators, and these reverse conditional probabilities can be easily obtained with Bayes' theorem and are standard in most statistical packages with a LCCA module (e.g., Mplus, Latent Gold, LEM).

Importantly, LCCA allows the researcher to evaluate the relative accuracy of competing diagnostic criteria in the absence of a "gold standard" (Faraone and Tsuang 1994; Young 1983). In other words, LCCA can be used to determine whether multiple definitions of a construct (e.g., vascular MDD) reflect a single underlying latent class or separate diagnostic entities. Latent class cluster analysis models also generate indices of sensitivity and specificity. For example, the probability of an indicator being present, given the presence of the illness, corresponds to the sensitivity of the indicator as a marker for the diagnosis. Similarly, the probability of an indicator being absent, given the absence of the illness, corresponds to the specificity of the indicator as a marker of the diagnosis (Young 1983). When the indicators are restricted to be dichotomous, LCCA becomes standard exploratory latent class analysis; when the indicators are continuous or mixed in type, the procedure is referred to variously as LCCA, latent profile analysis, or finite mixture modeling.

In contrast to LCCA, taxometric analysis does not start with the assumption that the latent structure of the construct is categorical. Rather, it starts with a test of whether the data are consistent with the assumption that the latent structure is dimensional and seeks to identify taxa or classes. Thus, taxometric analysis is a natural first choice for establishing a comprehensive program of structural research to determine the nature of boundaries in psychopathology (Ruscio and Ruscio 2004). According to Ruscio and Ruscio (2004), taxometrics requires large sample sizes (N = 300 minimum of combined taxon and nontaxon members) and a sufficient number of diagnostic features. The correlations among the indicators of these features must also be sufficiently large to be able to separate the putative taxon and complement class in order to detect the taxonic boundary should it exist. Thus, indicator correlations place constraints on the degree of between-group separation. As a result, although taxometrics is a natural first choice in a program of structural research, its use might be precluded in many instances because of the statistical requirements of the taxometric model.

The application of multivariate statistical techniques carries with it certain a priori assumptions that place restrictions on our ability to discern the "truth" about the nature of vascular MDD and limits the inferences we can make regarding its structure. For example, LCCA assumes that the structure of vascular MDD is categorical rather than continuous. Inferences back to the population of interest (i.e., vascular MDD patients) on the basis of data from clinical trials also carry with them certain assumptions. Patients who participate in clinical trials do not represent all vascular MDD patients, and differences in sampling (e.g., recruitment, inclusion and exclusion criteria) and measurement (including random error and systematic differences in measurement approaches) specific to each trial restricts generalizability. Thus, we must be careful not to misinterpret findings on the basis of clinical trial data as representing the population of vascular MDD patients in this formative period of diagnostic validation, especially because we have yet to identify what exactly defines that population. These multivariate statistical techniques are not new, and they are not viewed as a complete solution to problems inherent in psychiatric nosology (e.g., absence of a gold standard). Nevertheless, the approach we advocate (despite its inherent assumptions and limitations) might substantially improve on previous diagnostic efforts (e.g., expert consensus) through the application of a systematic, empirically-grounded, psychometric approach to evaluating diagnostic validity.

Significance

Establishing vascular MDD as a distinct diagnostic subtype of MDD in late-life has important implications for the process of defining potential disorders and their associated criteria. First, the systematic application of psychometric techniques such as LCCA and taxometrics stresses the importance of empirically identifying a distinct patient group that corresponds to the proposed diagnosis. Using these techniques to test hypotheses about alternative diagnostic criteria is a more empirically grounded approach to define diagnosis than previous DSM classification that has relied primarily on expert consensus. Second, unlike diagnostic criteria for other DSM disorders that have been based only on phenomenology, the defining features of vascular depression are likely to include laboratory values such as MRI hyperintensities or neuropsychological tests. Such biologically-based subtyping might lead to etiologically specific treatments with greater efficacy. Thus, vascular MDD might serve as a prototype for future psychiatric classification systems in which the content of the diagnostic criteria will be based both on phenomenology and laboratory values and the method of validation will be based both on evidence of internal and external validity.

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