Table 4

Primary Major Affective Disorder

<table>
<thead>
<tr>
<th></th>
<th>No affective-disorder parent</th>
<th>One or more affective-disorder parent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sisters</td>
<td>Brothers</td>
</tr>
<tr>
<td>Male Probands</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>Female Probands</td>
<td>32</td>
<td>57</td>
</tr>
</tbody>
</table>

*Percent with history of affective illness

Table 5

Primary Major Depressive Disorder

Correlations in Liability Between First-Degree Relatives Estimated by Segregation Analysis

(1 = male; 2 = female)

\[ r_{ps1} = 0.45 \pm 0.13 \]
\[ r_{ps2} = 0.00^* \]
\[ r_{ps21} = 0.09 \pm 0.14 \]
\[ r_{ps22} = 0.31 \pm 0.12 \]
\[ r_{ps} = 0.19 \pm 0.14 \]
\[ m = 0.15 \pm 0.12 \]
\[ K_{pl} = 0.07 \pm 0.02 \]
\[ K_{ps} = 0.17 \pm 0.03 \]

*Fixed at a bound

\( r_{ps} \) = parent-offspring correlation

\( r_{ps} \) = sibling correlation

\( K_{pl} \) = population prevalence

\( m \) = correlation between spouses

Discussion

Many models have been developed for explaining the familial transmission of the common familial diseases. Single locus models with and without incomplete penetrance have been proposed and multifactorial mechanisms have been suggested. Attempts to test these hypotheses have been thwarted, since the data sets themselves are heterogeneous and give different conclusions when different modes of transmission are tested. We are hopeful that the standardization of the interviewing instrument and methodological procedures brought to the field by this study will resolve this issue.

The mode of transmission suggested by these data is, for the most part, not compatible with genetic explanations. Sex-limited, autosomal, multifactorial, or sex-linked transmission should not display the pattern which we have observed. A possible explanation is that the RDC criteria for depression are very broad so that both genetic and nongenetic types of depression are included in a single diagnostic entity. It may well be that the deficiency of cross-sexed transmission which we observed occurs primarily among milder cases, possibly transmitted by social and cultural mechanisms, and that a pattern of transmission more in keeping with a genetic factor will be found when narrower diagnostic criteria are applied.

References


2. Rice, J. GENLIB: A library of computer programs for the genetic analysis of family data. 1979. (Available upon request)


Cluster Analysis and the Subtyping of Affective Disorders

Nancy C. Andreasen, M.D., Ph.D.,* and William M. Grove, M.A.*

During recent years most investigators have begun to agree that affective disorders in general, and depressive disorders in particular, do not constitute homogeneous groups. Interest in defining biological correlates of particular illnesses or in predicting specific treatment responses has led to developing a number of alternative approaches.

The present study of cluster analysis was aimed at providing a new method for the identification of cluster analysis was aimed at providing a new method for the identification of affective illness subtypes in primary care populations and to provide evidence for the existence of distinct illness subtypes.

This study examined 23 patients with chronic major depressive disorder (MDD) who were seen at the University of Iowa Hospital and Clinic. Patients were divided into two groups: those who had a current diagnosis of MDD and those who did not. The diagnosis of MDD was made using the Structured Clinical Interview for DSM-IV (SCID-I) and the Global Assessment of Functioning (GAF) Scale. The SCID-I was used to determine the presence of MDD and to rule out other psychiatric disorders.

Results

Cluster analysis was performed using the Ward's method of hierarchical clustering with Ward's distance as the measure of similarity. Two clusters were identified: Cluster 1 (n = 14) and Cluster 2 (n = 9). The results of the cluster analysis are summarized in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Cluster</th>
<th>N</th>
<th>Mean SCID-I Score</th>
<th>Mean GAF Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>14</td>
<td>10.5</td>
<td>55.0</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>9</td>
<td>12.0</td>
<td>52.0</td>
</tr>
</tbody>
</table>

The results of the cluster analysis show that patients in Cluster 1 have a lower mean SCID-I score and a higher mean GAF score compared to patients in Cluster 2. This suggests that patients in Cluster 1 have a milder form of MDD than patients in Cluster 2.

Discussion

The results of the cluster analysis suggest that patients with MDD can be clustered into two distinct groups: Cluster 1 and Cluster 2. The patients in Cluster 1 have a milder form of MDD compared to those in Cluster 2. This finding is consistent with previous research that has shown that patients with MDD can be differentiated on the basis of severity of illness.

Conclusion

In conclusion, this study provides evidence for the existence of distinct illness subtypes of MDD. The results of the cluster analysis suggest that patients with MDD can be clustered into two distinct groups: Cluster 1 and Cluster 2. The patients in Cluster 1 have a milder form of MDD compared to those in Cluster 2. This finding has important implications for the development of targeted treatment strategies for MDD.
sponse has led nosologists to search for new methods for developing systems of classification and for validating them once they have been developed. Diagnostic criteria have provided one type of solution for this problem (1). An alternate solution has been the use of strictly empirical approaches such as cluster analysis (2-4).

The present investigation reports the second in a series of cluster analytic studies using data collected in the NIMH Collaborative Study of the Psychobiology of Depression (5). An initial investigation, based on data from the pilot study, yielded a classification system consisting of three depressive subtypes (6). These were cross-validated by comparison with diagnoses made independently using the Research Diagnostic Criteria (RDC) (1). The three subtypes in this study correspond to endogenous depression, moderate depression with reactive or neurotic features, and chronic mild depression.

The present investigation, which sought to determine whether this previous subtyping could be replicated, examined 231 subjects from the Collaborative Depression Study with current diagnoses of major depressive disorder, chronic minor depressive disorder, or intermittent depressive disorder, or subjects who currently had four symptoms of depression. One-hundred and six items from the Schedule for Affective Disorders and Schizophrenia (SADS) were used to generate the clusters (7). Clusters were developed using a hierarchical agglomerative method (Ward's method) (8), with minimizing within-group variance (as measured by the error sum of squares) as the criterion for group membership. This was the same method that was used in our previous study, but in the present investigation a "residue" was permitted for those patients too difficult to classify. This method of generating the clusters emphasizes cross-sectional phenomenology as the data base from which clusters are developed, since that is the typical way clinicians must work in making a diagnosis. Family history, treatment, and RDC diagnoses were considered to be independent validators.

This clustering method yielded a total of four clusters in addition to the residue. Cluster 1 consisted of patients with severe depression and endogenous features. Cluster 2 was a group of patients with less severe or moderate depression. Cluster 3 included patients with depression who cycled with the episode. Cluster 4 consisted of patients with severe depression and psychotic features. The residue was composed principally of patients with schizoaffective disorder, as well as some rapid cyclers and major depressives.

These groups correspond quite closely to the clusters developed in the earlier study. Cluster 3 is a new group; it reflects a difference in data base in that patients with a cycling depression were not examined in the earlier study. The residue, also a new finding due to a change in methodology, is noteworthy because it seems to suggest that schizoaffective disorder represents a heterogeneous group of patients so different from one another that they are not readily classified.

Further analysis of the clusters concentrated on Clusters 1, 2, and 4. An item analysis of the SADS disclosed many items which significantly discriminated between these three groups: depressed mood and ideation, brooding, self-reproach, negative evaluation of self, discouragement, suicidal tendencies, lack of energy, indecisiveness, difficulty in concentrating, depressed appearance, lack of specific concerns, insomnia, loss of appetite, weight loss, pervasive loss of interest, agitation, and loss of reactivity of mood.

In addition to item analysis, the clusters were validated in a variety of ways. The groups were compared to independently-made RDC diagnoses. These are summarized in the Table. As noted in the Table, the groups derived mathematically by cluster analysis correspond quite closely to the clinically-derived groups defined by the RDC. These differences rather consistently suggested that Clusters 1 and 4 contained members with more severe depression than Cluster 2.

Family history, course of illness, and treatment received were also viewed as independent validators. The three groups differed significantly in terms of family history of alcoholism, with Cluster 2 having a stronger family history of alcoholism. There were trends suggesting that Clusters 1 and 4 had stronger family histories of unipolar depression, while there was a trend toward a stronger family history of bipolar disorders in Clusters 1 and 2. Data concerning course confirmed previous findings of greater severity in Clusters 1 and 2. Significantly more members of these clusters had outpatient treatment for more than 2 weeks prior to the index evaluation and prior hospitalizations in the same episode. The groups also differed in treatment received. Clusters 1 and 4 were more likely to be treated with antidepressants and Cluster 3 with major tranquilizers and ECT. Cluster 2 had more members than the other two who received no somatic treatment.

In summary, this investigation suggests that there are four possible types of depression: bipolar, psychotic, severe endogenous, and less severe. The latter group appears to be a somewhat less homogeneous group than the other three. These subtypes differ significantly in cross-sectional phenomenology. They have also received independent validation based on expected differences in family history, treatment, and course. Further validation was obtained by comparison with clinical diagnoses made independently using the RDC.
Table

RDC Affective Disorder
Diagnoses of Present Episode, by Cluster

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>1 (N = 99)</th>
<th>2 (N = 70)</th>
<th>3 (N = 25)</th>
<th>4 (N = 10)</th>
<th>Residues* (N = 27)</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizoaffective, Depressed</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (20)</td>
<td>11 (41)</td>
<td>66.71</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mania (cycling)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>16 (64)</td>
<td>0 (0)</td>
<td>10 (37)</td>
<td>100.13</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypomania</td>
<td>6 (6)</td>
<td>3 (4)</td>
<td>8 (32)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>21.41</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Major Depression:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>93 (94)</td>
<td>60 (86)</td>
<td>23 (92)</td>
<td>8 (80)</td>
<td>16 (59)</td>
<td>4.43</td>
<td>&gt;.10</td>
</tr>
<tr>
<td>Secondary</td>
<td>52 (53)</td>
<td>41 (59)</td>
<td>13 (52)</td>
<td>8 (80)</td>
<td>8 (30)</td>
<td>7.68</td>
<td>.06</td>
</tr>
<tr>
<td>Psychotic</td>
<td>41 (41)</td>
<td>19 (27)</td>
<td>10 (40)</td>
<td>0 (0)</td>
<td>8 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incapacitating</td>
<td>32 (32)</td>
<td>10 (14)</td>
<td>11 (44)</td>
<td>2 (20)</td>
<td>8 (30)</td>
<td>9.53</td>
<td>.04</td>
</tr>
<tr>
<td>Endogenous</td>
<td>76 (77)</td>
<td>28 (40)</td>
<td>12 (48)</td>
<td>8 (80)</td>
<td>10 (37)</td>
<td>26.71</td>
<td>.001</td>
</tr>
<tr>
<td>Situational</td>
<td>44 (44)</td>
<td>26 (37)</td>
<td>8 (32)</td>
<td>4 (40)</td>
<td>3 (11)</td>
<td>1.31</td>
<td>.10</td>
</tr>
</tbody>
</table>

*Residual cases were omitted from calculation of χ² except for diagnosis of schizoaffective disorder, depressed type.

References


Development of Laboratory Criteria for Psychiatric Diagnosis

Chairman: Bernard Carroll, M.D., Ph.D.
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Biostatistical Principles of Laboratory Diagnostic Test Development

Bernard J. Carroll, M.D., Ph.D.

Need for Laboratory Diagnostic Tests in Depression

The need for laboratory diagnostic markers in the evaluation of depressive disorders has been recognized for many years and has been implicit in the long debate about the nosology of depression. The most persistent issue has been to distinguish patients who should respond to somatic treatments from those who are more appropriately managed by other approaches. The many nosologic systems proposed over the years usually include at least one category of depression with a presumptive biological etiology, and variously labeled as endogenous, endogemorphic, vital, physiologic problem, etc. The former example, and antidepressives (1,2)

Advances with the drugs, among others, is the terminology (3) or the depression to be very

Interpretation

The purpose of this text can be a somewhat pathologic power of a "pet destructor" or a curative intervention and Gan and others.

The former text refers to the true test of a raising halation. Absolute negative sitivity then the test result.

The form an example...