Phenotyping type 2 diabetes and its psychiatric comorbidities: a deep learning analysis

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INTRODUCTION: Type 2 diabetes (T2D) is a condition with a high frequency of neuropsychiatric comorbidities that have different clinical profiles, prognoses, and treatments. Recently, four clusters of diabetes have been described by self-normalizing neural networks (SNNN): mild obesity-related diabetes (MORD), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild age-related diabetes MARD) [1] [2]. Each cluster may carry biological alterations with effects on the central nervous system (CNS) that could be associated with neuropsychiatric disorders and modify the psychopharmacological treatment profile [3][4].

AIM: to identify the neuropsychiatric comorbidities associated with each diabetes phenotype and calculate the probabilities of psychopharmacological treatment for each condition.

METHODS: Comparative cross-sectional study of outpatient adults with T2D who attended a multidisciplinary comprehensive care model [5]. Clinical characteristics and metabolic parameters were registered, and a diagnostic psychiatric evaluation was performed using the Mini International Neuropsychiatric Interview (M.I.N.I.). Diabetes clusters were classified using an SNNN model, and patients were classified in accordance with their psychiatric diagnosis.

Statistical analysis: normal distribution was assessed with the Kolmogorov-Smirnov test. The comparison between categorical variables was assessed using the $\chi 2$ test, and continuous variables were compared with the Mann-Whitney U. ORs were calculated with logistic regression analyses adjusted by sex and age.

RESULTS: We included 1735 subjects, 58% were women, with a median age of 59 years (IQR 52-66 years), the time since diagnosis was 1.5 years (IQR 0-3 years), and the median HbA1c was 7.3% (IQR 6.2-9.5%). Diabetes clusters showed the following distribution: 36.5% SIDD, 31.7% MORD, 22.3% MARD, and 9.3% SIRD. The prevalence of anxiety disorders was 19.1%, affective disorders 17.9%, and eating disorders 23.7%; a psychotropic medication was prescribed to 24.6% of the

patients. In the comparative analysis by diabetes clusters and sex, a higher prevalence of females was identified in all diabetes clusters (MORD 60.2%, SIDD 52.4%, SIRD 74%, MARD 57.4%; p<0.001). The MORD cluster reported the highest percentage of psychopathology compared to the other clusters (anxiety disorders 24.4%, affective disorders 20.4%, eating disorders 33.8%, psychotropic medication indication 29.8%; p<0.001). The SIRD cluster had the second highest percentage of eating disorders (30.4%) and psychotropic medication indication at 28.4% (anxiety disorders 17.3%, affective disorders 16%; p<0.001). While patients in the SIDD group had a higher percentage of affective disorders at 20.4% (anxiety disorders 17.9%, eating disorders 19.8%, psychotropic medication indication 23.1%; p<0.001). The MARD cluster was the cluster with the lowest percentages of psychopathology (anxiety disoirders14.5%, affective disorders 10.9%, eating disorders 13.2%, psychotropic medication indication 17.8%; p<0.001). OR for the presence of psychopathology were estimated according to the diabetes cluster; age and sex were used as covariates. The MORD cluster showed association with anxiety disorders (OR 1.4 [CI 1-1.8; p=0.019]) and eating disorders (OR 1.9 [CI 1.5-2.5; p<0.001]). The SIDD cluster had an OR 1.5 [CI 1-1.8; p=0.014] associated with affective disorders. Patients in the SIRD cluster had an OR 1.8 [CI 1.2-2.5; p<0.001] associated with eating disorders. The MARD cluster was associated as a protective factor against affective disorders (OR 0.6 [CI 0.4-0.8; p=0.009]) and eating disorders (OR 0.5 [CI 0.3-0.7; p=0.003]). Finally, we performed logistic regression analyses for each diabetes phenotype to evaluate the probability of pharmacological prescription for each group of psychiatric disorders. The four phenotypes of diabetes reported increased odds of having psychopharmacologic treatment for affective, anxiety, and eating disorders. Nonetheless, some of the associations were stronger for each phenotype. MORD patients reported higher odds of receiving a psychopharmacological treatment for anxiety disorders (OR 38.8 (CI 23-63), p<0.001). SIRD subjects had higher odds of treatment for affective disorders (OR 45.7 (CI 13-154), p<0.001). MARD patients had higher odds of treatment for affective disorders (OR 30.7 (CI 13-70), p<0.001). SIDD had higher odds of treatment for anxiety disorders (OR 25.8 (CI 16-41), p<0.001).

CONCLUSION: This study demonstrated differences in the presence of neuropsychiatric comorbidities and their probability for psychopharmacological treatment according to the diabetes phenotype. These results support a novel perspective of psychiatric comorbidities in diabetes, where psychiatric symptoms may be part of the syndromic spectrum of each diabetes phenotype with different neurobiological mechanisms. The consideration of diabetes phenotype would allow us to personalize the treatment and approach to each patient.

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