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Course of bipolar illness worsens after onset of insulin resistance

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ABSTRACT

Cross-sectional studies indicate that comorbid insulin resistance (IR) and type 2 diabetes are associated with a more severe course of bipolar disorder (BD); however, this relationship has not previously been assessed longitudinally. To address this, we reviewed health records of a case series of six patients with BD and comorbid IR. Severity and length of affective episodes (both mania and depression) over the lifetime were recorded using the Affective Morbidity Index; these data were obtained from ongoing prospective follow-up and from detailed retrospective chart reviews. All six patients with a previously episodic, relapsing-remitting course of illness experienced a worsening of morbidity after the onset of laboratory-demonstrated IR. These results suggest that IR may be a potential testable, modifiable factor in the progression of BD from a treatment responsive (episodic) to a non-responsive (chronic) course of illness.

1. Introduction

Over half of all patients with bipolar disorder (BD) have insulin resistance (IR) or type 2 diabetes (T2D) (Calkin et al., 2015; Mansur et al., 2016), independent of the effects of psychiatric medications (Henneman et al., 1954; Regenold et al., 2002). The development of T2D typically follows a progression of metabolic disturbance from euglycemia to insulin resistance (IR), to glucose intolerance, and eventually T2D. In our previous cross-sectional studies, we found that comorbid IR and T2D were associated with a chronic course of BD, increased rapid cycling, poor response to mood stabilizing treatment (Calkin et al., 2014, 2015, 2013; Ruzickova et al., 2003), cognitive impairment (Calkin and Alda, 2015), and adverse structural and chemical brain changes (Hajek et al., 2015, 2014). Similar results have since been independently reported (Mansur et al., 2016). Further, we found that patients with IR had *equally* poor outcomes as those with T2D (Calkin et al., 2015). These results raise the possibility that glucose metabolic state may be a testable prognostic factor and a potential target for intervention (Calkin et al., 2015). Intervention may be imperative, for once T2D manifests, it may no longer be possible to alter the clinical course, despite good glycemic control (Calkin and Alda, 2015).

No previous studies appear to have taken a longitudinal approach to examining the association between impaired glucose metabolism and course of BD. A single study (Goldstein et al., 2013) has prospectively assessed BD outcomes in relation to obesity – a risk factor for IR and T2D. Contrary to expectations, obesity was not found to predict the occurrence of depressive episodes in patients with BD during prospective follow-up (Goldstein et al., 2013). In our cross-sectional study of 186 patients, we found that patients with BD and elevated BMI had a more chronic course of illness and poor response to lithium (Calkin et al., 2009), but the direction of causality cannot be determined. Given the paucity of longitudinal evidence to date, it remains unclear whether IR/T2D are independently related to course of illness over time. In the present case series, we collected data from ongoing prospective follow-up and from retrospective chart reviews to recreate lifetime course of illness and associated morbidity in order to further assess the relationship between the onset of IR and change in course of bipolar illness.

2. Methods

Data were obtained for a case series of six patients with BD I and comorbid IR, for whom the most detailed medical records were available to obtain retrospective lifetime history from the time of onset of illness. All patients had a detailed psychiatric interview administered by a psychiatrist sub-specialized in Mood Disorders (CC), based on the Schedule for Affective Disorders and Schizophrenia, Lifetime version

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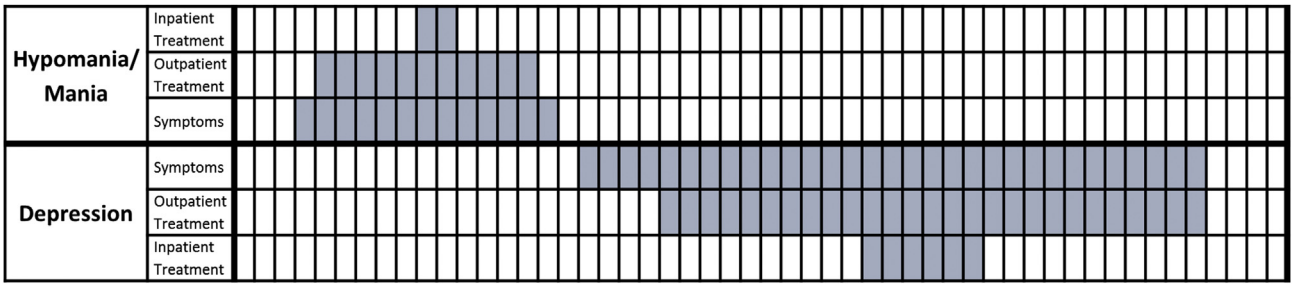

Fig. 1. Example Affective Morbidity Index (AMI) chart demonstrating course of illness over a one-year period. Each horizontal box represents one week and vertical boxes indicate severity of symptoms. In this example, the AMI is equal to 0.577, based on the following calculation: $\text{AMI} = \frac{(6 \text{ weeks with degree 1}) + (30 \text{ weeks with degree 2}) \times 2 + (8 \text{ weeks with degree 3}) \times 3}{52 \text{ total weeks} \times 3}$

(SADS-L) (Endicott and Spitzer, 1978), and diagnosis reached by consensus by the research team, as in our previous studies (Calkin et al., 2009; Ruzickova et al., 2003). The only exclusion criterion was absence of impaired glucose metabolism. No patients were excluded because of non-conformity with the proposed hypothesis. All patients provided informed consent for their data to be used in this study, which received approval from the Nova Scotia Health Authority Research Ethics Board.

Retrospective history over the lifetime of each patient was obtained by interviewing each patient and a family member, and by detailed review of all medical records prior to patients' prospective follow-up. This allowed for collection of data on severity and length of episodes of both mania and depression over the lifetime. These data were recorded using the Affective Morbidity Index (Coppen and Abou-Saleh, 1982) (AMI, see Fig. 1).

These patients have also been followed prospectively for two to seven years in the Mood and Metabolism (M&M) Program in Halifax, Canada. The M&M Program is a unique program with clinical and research components involving quarterly multidisciplinary assessments, including anthropometric and metabolic measures and daily mood ratings using the National Institute for Mental Health-Life Chart Method (NIMH-LCM) (Denicoff et al., 2000, 1997). The NIMH-LCM allows for prospective assessment of mood episodes; from these charts, associated morbidity was determined using the AMI (described in further detail below). Combining detailed retrospective and prospective data on illness episodes allowed us to reconstruct lifetime AMI for each patient from onset of illness to the present.

Insulin resistance was estimated by fasting plasma glucose (FPG) and concurrent fasting serum insulin (FSI) levels using the homeostatic model assessment – IR equation (HOMA-IR):

$$\text{HOMA-IR} = [\text{FPG (mmol/L)} \times \text{FSI (μU/mL)}]/22.5.$$

A cut-off of HOMA-IR ≥1.8 was used as the threshold for defining IR (Esteghamati et al., 2010). Fasting plasma glucose ≥5.7 mmol/L was considered elevated. The first recorded findings of IR or elevated FPG were correlated chronologically with the course of illness recorded on the AMI.

Assessment of outcome: Overall morbidity (pre- and post-onset of IR or elevated FPG) was calculated using the AMI. Severity was rated using three different degrees: symptoms that did not require a change in treatment were rated as 1; symptoms that required a change in outpatient treatment rated as 2; and symptoms requiring inpatient treatment rated as 3. The data were plotted on a chart (see Fig. 1 for an example); the absolute value of the area under the curve was then calculated and divided by the total number of weeks observed multiplied by the maximum severity of illness to give a fraction of maximum morbidity, referred to as the AMI.

$$\text{AMI} = \frac{(\text{weeks with degree 1}) + (\text{weeks with degree 2}) \times 2 + (\text{weeks with degree 3}) \times 3}{\text{Total number of weeks} \times 3}$$

Two AMI values were calculated: first, from onset of illness (Fig. 2, point a) to initial discovery of IR or elevated FPG (point b), and second,

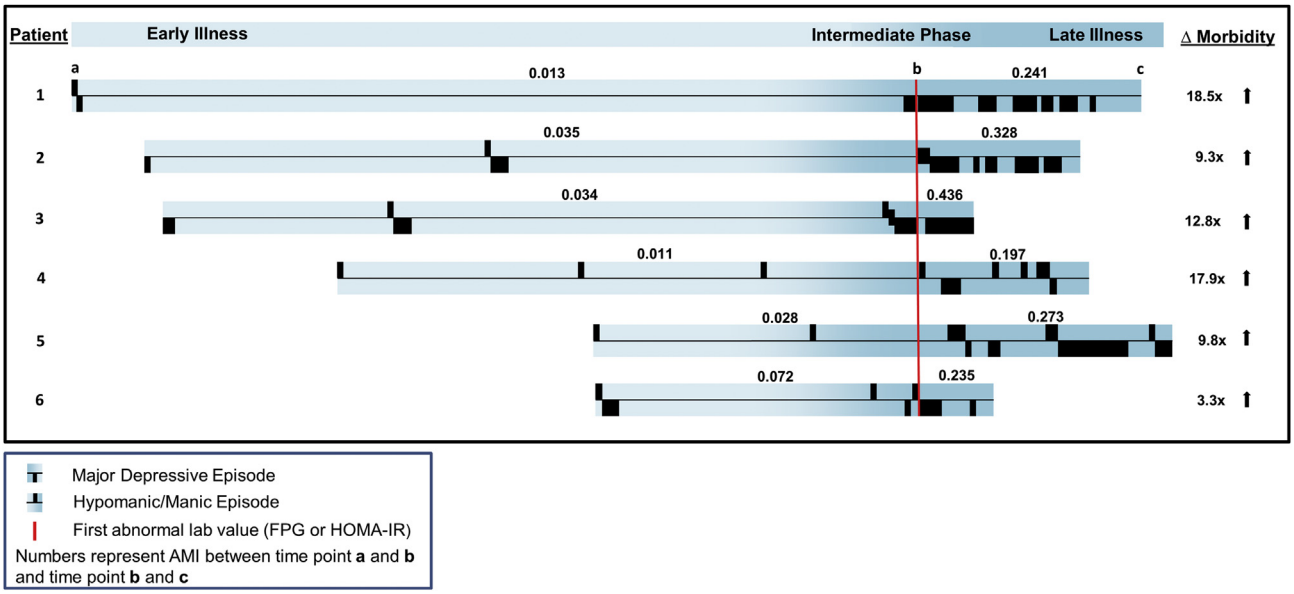

Fig. 2. Change in course of illness in six patients with bipolar disorder before and after the development of comorbid insulin resistance (red line), with increased morbidity (based on Affective Morbidity Index [AMI]) following the development of insulin resistance. FPG: fasting plasma glucose; HOMA-IR: homeostatic model assessment – insulin resistance. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)