Pharmacogenetics in psychiatry: Clinical case of resistant depression and a previous history of multiple adverse effects

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Dear Editor,

This article describes the case of a 43-year-old woman diagnosed with severe major depressive disorder. She presented her first depressive episode in 2004, during the postpartum period, and achieved apparent clinical recovery without medical consultation. In 2007, she visited the doctor for anxiety symptoms and started a treatment with paroxetine, which she discontinued after 3 days due to sedative effects. The same year, she was admitted to the acute psychiatric unit, because of a severe major depressive disorder with mood-incongruent psychotic symptoms. She was treated with venlafaxine 300 mg/d and quetiapine 150 mg/d, but she did not achieve complete remission. Two years later, in 2009, she re-entered the acute psychiatric unit and day hospital for a severe depressive relapse, and underwent treatment with electroconvulsive therapy (discontinued because of severe cognitive effects). Subsequently, she was followed in the outpatient clinic and she underwent different pharmacological strategies, including the following treatments: fluoxetine up to 40 mg/d, venlafaxine up to 375 mg/d, duloxetine up to 120 mg/d, clomipramine up to 225 mg/d, bupropion up to 300 mg/d, agomelatine up to 50 mg/d or trazodone up to 100 mg/d; augmentation with quetiapine up to 400 mg/d, aripiprazole up to 30 mg/d, paliperidone up to 3 mg/d, ziprasidone up to 120 mg/d, lithium carbonate up to 800 mg/d, lamotrigine up to 350 mg/d, topiramate up to 200 mg/d, thyroid hormone up to 50 mcg/d or methylphenidate up to 36 mg/d. Finally, she achieved remission of psychotic symptoms and partial improvement while she was on treatment with lamotrigine 350 mg/d and aripiprazole 20 mg/d, but she did not achieve a complete recovery.

A key factor, in the clinical management of this case, has been the difficulty in maintaining the prescribed treatment and to optimize dosage, because of side effects such as: weight gain and drowsiness (quetiapine, clomipramine), gastrointestinal side effects (bupropion, duloxetine), hematomas (fluoxetine), distal tremor (methylphenidate), akathisia (paliperidone) and possible esophageal dystonia (aripiprazole 30 mg/d, which remitted when reduced to 20 mg/d).

Pharmacogenetic testing: In February 2015, the patient underwent Neuropharmagen®[1,2] testing. Test results revealed that the patient has a genotype compatible with an intermediate metabolism for CYP2D6, indicating a possible reason for the tolerability problems and side effects to many antidepressants and antipsychotics used. So, this result confirms the clinical evaluation done during the follow-up. On the other hand, the test highlighted the possibility of favorable response and low likelihood of side effects with escitalopram, as results indicated the presence of a genetic variant in the *ABCB1* gene associated with a higher probability of positive response to this treatment[3].

In addition, escitalopram is mainly metabolized by the CYP2C19 pathway, it is a minor substrate of CYP2D6 and its main active metabolite is only partially metabolized by CYP2D6, therefore it would be less likely that the patient presents tolerability issues.

The test also indicated a higher chance of favorable response to lamotrigine, because the patient is not a carrier of a genetic variant in *ABCB1* associated with drug resistance to several mood stabilizers in polymedicated adult patients[4].

From October 2014, the patient had been treated with escitalopram 10 mg/d and, considering the test results, it was decided to optimize the dose up to 20 mg/d. Lamotrigine 350 mg/d was maintained, while aripiprazole dose was reduced to minimize side effects, since this drug is primarily metabolized by the CYP2D6 pathway. The patient was assessed frequently without presenting exacerbation of psychotic symptoms.

After 3 months of following the Neuropharmagen® recommendations, the patient scored 2 (much better) for the Patient Global Impression of Improvement (CGI-I) scale. Also, side effects were assessed with the FIBSER questionnaire (which reviews the frequency, intensity and burden of side effects). In the initial evaluation, the patient displayed side effects with a frequency of 50%, an intensity of 4 out of 6, and presented many limitations in relation to those side effects. However, after 3 months, these side effects were present only 10% of the time, with an intensity of 0 out of to 6.

Discussion

For this clinical case, the results of the pharmacogenetic test allowed the identification of an optimal treatment with a lower probability of side effects, in a patient who had

presented a large history of adverse drug effects for most of the medications tested.

Specifically, the test results led to a dose increased of escitalopram, something that had not been done previously because of the patient's history of low tolerability to psychiatric medications. Also, it led to a decrease in aripiprazole dose, which improved tolerability without exacerbation of psychotic symptoms.

The test result will be useful in the future management of this patient. Considering that escitalopram is a moderate inhibitor of CYP2D6 enzyme and that the patient has an intermediate cytochrome function, caution should be necessary. Specially, if combined with other drugs with a narrow therapeutic range that are metabolized by this enzyme (antidepressants such as venlafaxine, fluoxetine, clomipramine, nortriptyline, or antipsychotics such as risperidone or haloperidol). If a combination was necessary, a dosage adjustment should be considered.

Probably, if the pharmacogenetic test had performed at an early stage, it would have been possible to optimize treatment at the beginning, so the risk of progression to chronic disease and the residual symptoms could had been reduced.

ACKNOWLEDGEMENTS

AB-Biotics, S. A., Barcelona, Spain (Drs J. Espadaler, M. Tuson, L. Viladevall)

CONFLICTS OF INTEREST

E. Aguilar has received grants and served as consultant, advisor or CME speaker for Janssen Cilag and Lundbeck/Otsuka. J.A. Monreal has received grants and served as consultant, advisor or CME speaker for Janssen Cilag, Sanofi-Aventis and Servier. D.J. Palao has received grants and served as consultant, advisor or CME speaker for Lundbeck/Otsuka.

E. Aguilar, J.A. Monreal and D.J. Palao have participated as a collaborator researcher in a multicentric clinical. Promoter: AB-BIOTICS S.A. Registered at EudraCT (identifier: 2013-002228-18) and at ClinicalTrials.gov (identifier: NCT02529462).

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Application of stem cells to the knowledge and treatment of psychiatric diseases

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Dear editor,

The knowledge of the biological basis of neuropsychiatric diseases has made great progress in the last decades. It has been possible to characterize genetic modifications present in several psychiatric disorders that could be potential targets for the development of new treatments for mental illness[1]. In addition, the advances in the identification of changes in the expression of small non-coding RNAs (micro-RNAs) in biological fluids of psychiatric patients will provide objective criteria to establish the diagnosis and prognosis of mental diseases and to evaluate the therapeutic efficiency of current treatments of psychiatric pathologies[2]. The progress in the knowledge of the stem cells as possible therapeutic and / or diagnostic tools have been added to this hopeful scenario. The aim of this short assay is to highlight three major aspects derived from the study of neural stem cells biology of major impact in the understanding of mental illness and its treatment.

Human brain organoids as models of neuropsychiatric disease

Animal models of human mental diseases have unques-

tionable limitations to transfer the results of their study to the clinical practice. Therefore, developing an accurate and powerful biological model for neuropsichiatric disorder has been a major challenge in modern psychiatric research. The application of induced pluripontent stem-cell (iPSC) technology has generated a new experimental paradigm by obtaining neurons growing in vitro from experimentally reprogrammed cells obtained from psychiatric patients.

iPSCs are obtained from adult tissues (dermis, hair follicles, etc.) by transfection of a cocktail of genes that reprogram them and makes them pluripotent, that is, capable of differentiating in vitro into different cell lineages, including neurons. Differentiation into neurons of different types (motor, dopaminergic, etc.) is achieved by using well defined culture protocols. By this procedure (two-dimensional cultures) it was observed that neurons from subjects with bipolar disorder, schizophrenia or autistic spectrum disorders show alterations in their morphology and connectivity[3] that can be abrogated by drug therapy[3,4] or genetic modifications. This in-vitro approach has been implemented by modifying the physical conditions of the culture so that the neurons instead of growing on the surface of the culture dish do so in small masses of tissue that grow in the three dimensions of the space. These three-dimensional cultures are termed" cerebral organoids" and allow differentiation of distinct types of neurons that establish circuits resembling human brain tissue[3]. This new experimental setting, has been employed to evaluate the effect of genetic manipulations or pharmacological treatments designed to modify the structural alterations present in neuronal cultures made from patient´s iPSCs[3,5,6,7].

Among the findings obtained by this new methodology it can be emphasized neuroplasticity phenotypic changes in hippocampal neurons of patients with bipolar disorder in relation to healthy controls[8]. Martens et al[9] have reported that hippocampal neurons (iPSCs) from patients with bipolar disorder were "hyper excitable". This hiperexcitabilty was selectively reversed by lithium treatment only if neurons derived from patients who also responded to lithium, but not if they derived from patients who were resistant to it. Hence, the electrical activity of these cultures could be used in the future to predict the response to lithium treatment.

Using this methodology, it has been also detected, deficiencies in interneuronal connectivity in neurons from schizophrenic patients[10] that are diminished by adding the antipsychotic loxapine to the culture medium. Similar experimental approaches have also been used to design specific therapies for autism spectrum disorders[11]. The cultures of neurons obtained from iPSCs of patients with idiopathic autism spectrum disorders showed abnormal behaviour and structural alterations that were diminished by IGFL1 growth factor treatments[12], a growth factor whose therapeutic application is being analysed in conventional clinical trials.

Overall, the above discussed experiments illustrate how this new methodology will allow major advances in the knowledge of psychiatric pathology and treatment.

Neurogenesis and psychiatric pathology

The central nervous system of adult mammals contains well defined zones, termed "niches", of neural cell progenitors capable of replacing both glia and neurons. In the adult human brain, two well-defined regions of neurogenesis have been identified, the sub-ventricular zone on the antero-lateral wall of the telencephalic ventricles (V-SVZ niche) and the sub-granular zone of the dentate gyrus in the hippocampal complex (SGZ niche). In children, the sub-ventricular zone generates neuroblasts that migrate to replace the olfactory bulb neurons, and in the adult, it mainly produces interneurons of the striatum[14]. On the other hand, the sub-granular area of the dentate gyrus can replace granular neurons of the hippocampal complex. There is evidence that the SGZ niche is affected in human depressive illness and in animal models of depression or anxiety[15]. In addition, both the administration of antidepressants drugs[16] and electro convulsive therapy[17] promote neurogenesis in the dentate gyrus but treatment lose its antidepressant effect if the niche SGZ is removed by genetic manipulation or ionizing radiation[18].

Some studies indicate that deficiencies in adult neurogénesis are more characteristic of schizophrenia than depression[19,20], but in this case alterations are present in the V-SVZ niche[21].

Knowledge of changes in neurogenesis in other psychiatric diseases is scarce. In alcohol consumers, neurogenesis is altered and may contribute to the pathology associated with alcoholism[22]. The same seems to happen with other addictive substances[23].

Cell therapy in psychiatric pathology

A well-known fact in schizophrenic patients is the decrease in brain volume, neuronal size, and dendritic spine density and other alterations in prefrontal cortex. Accordingly, attempts to develop cellular therapies in murine models of this disease have been published[24]. Thus, the graft of GABAergic interneurons from healthy donors into the prefrontal cortex of neonatal mice makes them resistant to the schizophreniform cognitive deficits induced by phencyclidina[25]. However, despite the progress in obtaining interneurons from embryonic stem cells or from iPSC[10], the applicability of this therapeutic approach to humans is still far away. Cell therapy has been used also as a therapeutic approach for autistic spectrum disorders, but in this case not for regenerative purposes but on the basis of the anti-inflammatory properties of stem cells[26].

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