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A PHARMACOGENETIC-DRIVEN APPROACH IN TWO SEVERELY ILL NON-RESPONDER ADOLESCENT PSYCHIATRIC PATIENTS

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pharmacogenetics, adolescent, mental health

Introduction

Evidence is growing that pharmacogenetic outcomes are related to drug resistance. We undertook genetic tests in order to study pharmacogenetic variables in two severely ill adolescent patients who were resistant to therapy. These two patients had different psychiatric conditions (patient A with attention deficit and hyperactivity disorder, patient B with bipolar disorder). They presented at baseline with adverse events related to current psychopharmacological treatment. By using a pharmacogenetics test we were able to ascertain which medications would be most suitable for safely and effectively treating the patients. To that aim, we used the commercially-available Neuropharmagen test (AB-BIOTICS S.A, Barcelona, Spain), that evaluates genetic polymorphisms of pharmacogenetic relevance in 30 different genes, including all major cytochromes. The Neuropharmagen test was previously studied in epileptic patients [1] and has recently been shown to increase the odds of improvement and stabilization in psychiatric patients with different conditions, when compared to treatment as usual in a naturalistic setting [2].

Case Report

Patient A is a 16 year-old adopted boy, who presented to our inpatient unit with aggression, opposition, violent behavior and cannabis abuse. The history of substance abuse is not surprising since it have been associated with higher rate of misuse of stimulants in college students afflicted by ADHD [3]. He lived in South America until the age of 4 and then he moved to Italy. There was little anamnestic information, except for a report of a family history of unspecified neuropsychiatric disorders. One year before the current hospitalization he was diagnosed with conduct disorder and attention deficit and hyperactivity disorder (ADHD). Given the high severity of his clinical condition, at that time he was seen by the territorial service and was administered valproic acid (500 mg/die), gabapentin (300 mg/die) and risperidone (3 mg/die). He was still taking these medications when we saw him. However, he had suffered various adverse events related to the pharmacological therapy assumed, in particular somnolence, excessive weight gain and

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extrapyramidal symptoms. We therefore decided to undertake a pharmacogenetic evaluationin order to make further therapeutic choices. The results of the pharmacogenetic evaluation showed a higher risk of developing adverse events with some drugs (among which were risperidone and valproic acid), together with a higher probability to respond to other drugs (such as methylphenidate and aripiprazole). So, we decided to discontinue his therapy and to switch to methylphenidate (20 mg/die) and ariprazole (20 mg/die). The Recommendations on methylphenidate are based on genetic variants in LPHN3 [4] and CES1 gene [5]. After 3 months the patient's illness was much improved (score: 2) according to the Clinical Global Impression – Improvement scale (CGI-I). At the same time, the patient did not reported any adverse event.

Of course, the response to metylphenidate could have been surely related to the fact that this medication represents the treatment of choice for ADHD; however, we went for that treatment, otherwise not necessarily indicated in this case, following the indications of the pharmacogenetics test. Indeed, patient A presents an history of substance abuse which in college students with ADHD is associated with higher rate of misuse of prescription stimulants [5].

Patient B is a 15 year-old boy, who presented to our inpatient unit with insomnia, anxiety, grandiosity, accelerated thought processes, command hallucinations, delusions of reference, and hyperactivity. He was diagnosed as bipolar I, in a manic phase with psychotic symptoms. He was then administered risperidone, which was increased up to 4 mg, with only partial benefits and with the onset of adverse events, namely somnolence and weight gain. As in the previous case of drug resistance, we performed a pharmacogenetic evaluation by using the Neuropharmagentest in order to optimize the therapeutic choices. The results of the pharmacogenetic evaluation showed a higher risk of developing adverse events with some antipsychotics (including risperidone) and a higher probability to respond to other medications (including aripiprazole and lithium). Neuropharmagen analyses base the good response to lithium on the rs2284017 polymorphism of the CACNG2 gene, in agreement with findings obtained in 2 independent cohorts [6]. The selection of aripiprazole as a suitable medication is instead based on the assessment of 28 different haplotypes in gene CYP2D6. Indeed, the decreased activity of CYP2D6 significantly impairs the metabolism of aripiprazole, and the FDA currently recommends reducing the dose of aripiprazole to 50% of the standard dose in patients that are poor metabolizers of CYP2D6 (FDA-approved labelling from June 2014). Moving from these evidences, we decided to discontinue his therapy and to switch to carbolithium (900 mg/die) and aripiprazole (20 mg/die). As for patient A, the CGI-I scored 2, much improved, after 3 months of therapy and the patient had a partial remission of symptomatology, with a reduction of psychotic symptoms, and a consistent reduction of hyperactivity, anxiety and accelerated thought processes. Moreover, patient B did not have any adverse event following the pharmacogenetic-driven therapy.

Discussion

Adolescent psychiatric patients are among the most challenging to treat, and many of them undergo several different treatment regimens before showing improvement. Adverse drug reactions and lack of effect often lead to adherence problems, which further dampen the chances of achieving a good control of the condition, as well as to frequent changes in medication and higher drug costs.

Researchers are starting to develop clinical guidelines on how to make use of pharmacogenetic testing [7-9]. The implication is that just as family history or plasma levels can help predict the efficacy of any particular drug, the genetic background of a patient can also be used to help determine expected drug response. Indeed, the results presented herein are in line with a previous study analyzing the effect of pharmacogenetics in hospitalized pediatric psychatric patients [10]. However the pharmacogenetic approach remains in a very promising but pioneering stage, and the variance explained so far is modest.

In conclusion, we believe further research on this topic is warranted, so that clinical recommendations can be issued. We consider pharmacogenetic information could be especially useful in difficult to treat cases, such as polymedicated patients not responding to therapy, as per the two cases reported herein.

Take home messages for psychiatric care

- Evidence is growing that pharmacogenetic outcomes are related to genetically driven drug resistance
- Researchers are starting to develop clinical guidelines on how to make use of pharmacogenetic testing
- Pharmacogenetic information could be especially useful in difficult to treat cases, such as polymedicated patients not responding to therapy
- Pharmacogenetic approach remains in a very promising but pioneering stage

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