Somatic Complications of Psychotropic Medications in a Patient with Multiple CYP2 Drug Metabolism Deficiencies

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ABSTRACT—A 54-year-old woman presented with severe anxiety, multiple somatic complaints, medication intolerance and adverse drug reactions (ADRs) to numerous prescribed psychotropic medications. Multiple drug metabolizing deficiencies were suspected. Molecular analysis was performed for the CYP2 family of Cytochrome P450 (CYP450) drug metabolism isoenzymes by DNA typing CYP2D6, CYP2C9, and CYP2C19 genes. A multiple deficiency in CYP2 drug metabolism was discovered. The patient was a double carrier of null alleles for CYP2D6, a carrier of a null allele for CYP2C19 and a carrier of a deficient allele for CYP2C9. These alleles were confirmed by Mendelian inheritance in her nuclear family, where her brother had a similar multigene CYP2 deficiency. The patient improved clinically with discontinuation of psychotropic medications, suggesting that much of her symptomatology was drug-induced. DNA typing for multigene CYP2 deficiencies is diagnostically useful in individuals with histories of multiple ADRs, which could be avoided by DNA-guided individualized prescription.

Introduction

OVER 100,000 ADRs occur annually and 17% of such patients require hospitalization at an estimated cost of 182 billion dollars.\textsuperscript{1,2} A significant portion of these ADRs may be attributable to the many drugs metabolized by the highly polymorphic Cytochrome P450 (CYP450) enzymes.\textsuperscript{3} The isoenzymes are highly variable in human populations.\textsuperscript{4} The principal CYP450 enzymes whose function can be predicted from genetically inherited mutations and polymorphisms are CYP450 genes CYP2D6, CYP2C9 and CYP2C19, which are predominantly expressed in the liver. The heterogeneous drug metabolism phenotypes are predictable for each person from inherited CYP2 gene alleles, ranging functionally from ultrarapid to null metabolizers.\textsuperscript{5}

Extremes of function have the most potential clinical impact. A case of intoxication by codeine, a prodrug activated by CYP2D6 metabolism, has been reported in an ultrarapid metabolizer patient.\textsuperscript{6} In that report, a patient was identified by DNA typing as a carrier of CYP2D6 gene duplications. In contrast, we present the case of a patient profoundly deficient in drug metabolism capability by virtue of being a carrier of multiple null and deficient alleles in CYP2D6, CYP2C9, and CYP2C19. The case demonstrates that DNA typing is a powerful tool to identify and prevent adverse drug reactions to psychotropic medications.\textsuperscript{7-9}

Case Report.—A 54-year-old Caucasian woman presented with a history of persistent malaise, headache, muscle tension, jaw clenching, severe anxiety and hypervigilance. She had become increasingly preoccupied with her somatic condition, had stopped working as a well-paid, self-employed marketing consultant, and had withdrawn from many of her usual activities and interests. She denied...
a prior psychiatric history. The patient’s family history was significant for attention deficit disorder in her brother and for anxiety and adverse drug reactions in her mother.

The patient’s difficulties had developed six years prior to evaluation after the improper installation of a home heating system that allowed volatile fuels and products of combustion into the home. She subsequently sought diagnosis and treatment for intermittent symptoms including a burning, metallic taste, dry mouth, nausea, vomiting, diarrhea, flatulence, excessive sweating, weight gain, insomnia, akathisia, muscle twitching, a “crawling feeling” beneath her skin, paraesthesias, and cognitive “fogginess.” During several interviews she was noted to be a pleasant, articulate woman with superior intelligence. Affect was labile with significant tearfulness, anxiety and hypervigilance. She denied depressed mood but admitted to occasional feelings of hopelessness. She was never suicidal or homicidal.

There was no evidence of mania, hypomania, psychosis, or cognitive abnormalities in her history. Speech was coherent, relevant, logical, and goal directed. She had been told that her symptoms were those of a generalized anxiety disorder. She had entered psychiatric treatment with several psychiatrists and psychotherapists in succession.

Pharmacotherapy included, over the six-year period, the following psychotropic classes and 18 specific drugs individually or in combination: seven antidepressants (citalopram, escitalopram, mirtazapine, norortryptiline, paroxetine, sertraline, venlafaxine XR); three antipsychotics (olanzapine, quetiapine, risperidone); three anticonvulsants (gabapentin, oxcarbazepine, topiramate); and five anxiolytics (buspirone, clonazepam, diazepam, flurazepam, lorazepam). While taking nortryptiline, 75 mg/day, her serum nortryptiline level was 257 ng/ml, approximately two to three times higher than the therapeutic reference interval at that dosage (50–150 ng/ml).

By the time she presented to her current psychiatrist, it was difficult for her to distinguish original symptoms from new ones and from the possible side effects of medications themselves. The possibility of deficiencies in drug metabolizing capacity was considered clinically as a result of multiple adverse drug reactions. The patient was referred for DNA typing of CYP2D6, CYP2C9 and CYP2C19 drug metabolizing enzymes. DNA was extracted from whole blood for CYP2D6, CYP2C9 and CYP2C19 DNA typing as previously described.10–12

Results

DNA Typing.—The genotypes observed in the proband and her family are shown together with their predicted phenotypic changes and metabolizer properties in Table 1. The patient was a double carrier for the CYP2D6 frameshift allele *6, which is a null allele. Being a double carrier of this allele, the patient lacks any CYP2D6 enzyme activity. She was also a carrier for CYP2C9 deficient allele *3 and for CYP2C19 null allele *2. Being a single carrier of these alleles, with a compensating functional copy, the predicted phenotype for both CYP2C9 and CYP2C19 is subnormal (Fig. 1). The patient is thus multiply compromised for drug metabolizing capacity in the three CYP2 genes analyzed.

To confirm the proband’s alleles, the patient’s parents and brother were also typed. Mendelian inheritance was confirmed for each allele (Fig. 2). For the CYP2D6 gene, both parents are carriers of the *6 null allele and the proband is a *6 double carrier. Her father is also a carrier of the CYP2D6 splicing defect allele *4 and therefore lacks any CYP2D6 enzyme activity. Similarly, her brother is a carrier of CYP2D6 null alleles *4 and *6, and lacks any CYP2D6 enzyme activity. For the CYP2C9 gene, the father is a carrier of deficient alleles *2 and *3, and the mother of the *2 allele. The proband is a CYP2C9 *3 carrier. Notably, the brother is also a carrier of CYP2C9 deficient alleles *2 and *3. For the CYP2C19 gene, the mother is a carrier of null allele *2, as is the proband.

The proband had the most functionally compromised combination of alleles assorting in her family. Both her father and brother are normal for CYP2C19 activity whereas she is deficient. Her mother is deficient for CYP2D6 activity whereas the proband lacks any.

Clinical Course.—When the patient first presented to her current psychiatrist she was taking sertraline 25 mg QD, which was being tapered from a higher dose, and escitalopram 2.5 mg QD, which had been started two days previously. She was also occasionally using low dose diazepam. While awaiting CYP2 DNA typing results, the escitalopram was discontinued, sertraline was continued, and mirtazapine started to a maximum dose of 30 mg QHS. It became quickly apparent that the patient was intolerant to mirtazapine.
When the CYP2 DNA typing results became available, sertraline, mirtazapine and diazepam were immediately tapered over a four-day period and discontinued. She was simultaneously placed on gabapentin up to a dose of 200 mg QID and lorazepam up to a dose of 0.5 mg QID both of which added partial benefit. Buspirone was briefly used in a dose of 15 mg BID. However, because of lack of clinical effectiveness, gabapentin, lorazepam and buspirone were later also discontinued in favor of clonazepam, which the patient remembered being the most helpful of her previous medications. She is currently taking clonazepam 0.5 mg QAM and 1 mg QHS.

A significant subset of her symptoms gradually disappeared over a two-month period once medications metabolized by CYP2D6, CYP2C19 and CYP2C9 were avoided. Prior symptoms still in remission several months later included the burning, metallic taste, dry mouth, nausea, vomiting, diarrhea, flatulence, excessive sweating, a crawling feeling under her skin, paresthesias, “electric shocks” in her extremities, eye twitching, muscle twitching, akathisia, and cognitive “fogginess.” Her Hamilton Anxiety score was reduced from 32 to 12 (measured retrospectively when asked to recall the time that she felt the worst). At the present time the patient reports a significant improvement in the clarity of her thinking and reduced anxiety. Her family has noted that she “seems like her old self.”

**Discussion**

We present a case in which the discovery of multiple cytochrome p450 enzyme deficiencies in a patient resulted in a dramatic change in treatment approach. Of the 18 medications she had taken, those in which CYP2 metabolism is involved included 10 drugs: citalopram, escitalopram, mirtazapine, nortriptyline, paroxetine, sertraline, venlafaxine XR, olanzapine, risperidone, and diazepam (Table 2). The patient is genetically deficient in the capacity to
metabolize each of these drugs and thus warrants a smaller dose and close monitoring for adverse drug reactions. Drugs not metabolized by CYP2 isoenzymes included quetiapine, gabapentin, oxcarbazepine, topiramate, buspirone, clonazepam, flurazepam, and lorazepam.

Heretofore, analysis of drug metabolism capacity based on single enzymes and receptors has laid the foundation for much of pharmacogenetics. Parallel DNA typing of several genes coding for drug metabolizing isoenzymes may reveal sensitivities observed only in multiply deficient individuals. The prevalence of double carriers of null alleles is 5% for the CYP2D6 gene. When these CYP2D6 null metabolizers are compounded with their simultaneous status as carriers of deficient or null alleles for both CYP2C9 and CYP2C19 genes (25% prevalence each), the carrier prevalence of triple deficiencies, such as the proband, can be estimated at ~0.3% based on our population surveys. The severity of the patient’s reaction to the exposure to volatile fuels and combustion products has aspects consistent with Multiple Chemical Sensitivity.15,16

We believe the definition of a novel drug sensitivity syndrome is warranted in carriers of multiple null and deficient alleles of CYP2 genes. Independently segregating alleles have the additional property of sporadic, nonfamilial, concurrence in an individual depending on chance. Such individuals are multiply deficient in CYP2 metabolic routes, which places them at risk for adverse reactions with several pharmaceuticals. That one out of 300 patients may be severely compromised for CYP2 drug metabolism in general should serve as a public health imperative for the wide use of DNA typing as an adjunct of pharmacotherapy. As the field of personalized medicine advances, we foresee DNA-guided pharmacotherapy being used to prevent adverse drug reactions.17

REFERENCES

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