Biological Psychiatry

Paradoxical Improvement of Schizophrenic Symptoms by a Dopaminergic Agonist: An Example of Personalized Psychiatry in a Copy Number Variation–Carrying Patient

To the Editor:

Compelling evidence suggests that rare variants, such as copy number variations (CNVs) (1) or single nucleotide variation, can result in psychotic disorders (2). Studying phenotypic correlates of specific genotypes could shed light on the substrates underlying functional alterations, including cognition, which remains the most disabling domain for patients with schizophrenia (3). It could also guide specific treatment strategies, combining pharmacologic and nonpharmacologic interventions. We report a young patient with atypical psychosis carrying a de novo duplication (dup17p13.3) in whom dopaminergic agonists alleviated psychotic symptoms and improved cognitive functioning.

Schizophrenia was initially diagnosed in a 20-year-old Caucasian woman who fulfilled DSM-IV-TR criteria as screened with the standardized Diagnostic Interview for Genetic Studies (DIGS-3.0) (4). Prominent manifestations were major functional decline; disorganization of thought; hermetic, circumstantial, and diffluent speech; unusual beliefs (e.g., interest in divination); and cognitive dysfunctions, especially slowness, attentional and executive alterations, instrumental disabilities, and theory of mind deficit, but no overall intellectual deficiency (Table 1). Attentional deficit was present in childhood. Antipsychotics (aripiprazole 10 mg or quetiapine 150 mg) worsened apathy and provided no clinical benefit. In addition to resistance to treatment, atypical clinical features included childhood behavioral abnormalities (tantrums, heteroaggressivity), learning disorders (reading and calculation), and morphologic features (microcephaly, microretrognathism, mild strabismus, marfanoid habitus). The neurologic examination was normal except for synkinesis.

Laboratory investigations were within the normal range (including homocysteinemia, B9 and B12 vitamins, amino acid chromatography, prolactinemia, autoimmunity screening). However, a 60K array comparative genomic hybridization identified a de novo duplication on chromosome 17 (dup17p13.3), with boundaries of the duplication (726,655–1,419,362) [hg19] including 10 genes (*NXN* [Online Mendelian Inheritance in Man (OMIM) 612895]; *TIMM22* [OMIM 607251]; *ABR* [OMIM 600365]; *MIR3183*, a microRNA without known brain target; *BHLHA9* [OMIM 615416]; *TUSC5* [OMIM 612211]; *YWHAE* [OMIM 605066]; *CRK* [OMIM 164762]; *MYOC1* hypothetical gene; *INPP5K* [OMIM 607875]). Brain magnetic resonance imaging and echocardiography were normal.

Among these genes, only *YWHAE* (also called tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon gene) encoding the 14-3-3-epsilon protein has previously been implicated in neuropsychiatric conditions (5), including schizophrenia and attentional deficit. This protein has multiple functions including the regulation of the key enzyme in dopamine synthesis, tyrosine hydroxylase, by modulating phosphorylation on serine 40. It is reasonable to speculate that duplications of *YWHAE* can influence tyrosine hydroxylase stability and dopamine synthesis (6). During medication withdrawal, we explored dopamine transmission. Homovanillic acid, the main dopamine metabolite, was markedly decreased in the cerebrospinal fluid (84 nmol/L; normal range, 156–410 nmol/L), whereas the level of tyrosine, the precursor, was in the normal range (11 μmol/L). The serotoninergic pathway was not impacted, with a normal level of 5-hydroxyindoleacetic acid (78 nmol/L; normal range, 63–185 nmol/L). DaTSCAN, performed in Pitié-Salpétrière Hospital, Paris (triple-head camera equipped with high-resolution parallel collimators [IRIX; Philips Medical, Cleveland, Ohio]), was normal, thus excluding a problem with dopaminergic receptors. Altogether, these arguments supported a deficit in dopamine synthesis in this patient.

To counteract the dopamine deficit, we introduced methylphenidate, gradually titrated over 8 months up to a maximum dose of 54 mg. Attentional symptoms were partially improved, as confirmed by Conners' Adult ADHD Rating Scales. However, the patient stopped medication because she felt no subjective improvement. We further tried a dopaminergic agonist (slow titration of pramipexole to .44 mg/day). Pramipexole, as an adjunct to antipsychotics, benefitted a subset of patients (7). In this patient, a partial clinical improvement was observed with pramipexole alone, especially in interpersonal interactions and disorganization as shown by interviews recorded and blindly scored by two clinicians (GM, IA) using the scale for the assessment of Thought, Language and Communication before pramipexole intake (score 31) and 2 hours after pramipexole intake (score 14). To potentiate the effect of medication, we elaborated a personalized and integrated care strategy that combined cognitive remediation programs for executive and attentional disorders, social cognition disorders, and calculation disturbances. This joint strategy improved the patient's clinical symptoms and her cognitive functioning after 32 weeks of care (Table 1).

In this young woman with an initial diagnosis of schizophrenia, atypical clinical features prompted us to conduct complementary explorations. We identified a de novo CNV (dup17p13.3), a rare duplication (.021% in patients with neuropsychiatric conditions vs. .006% in control subjects; 50% of them being de novo) previously associated with autism spectrum disorder (8,9), developmental delay (1), and schizophrenia (1). Three different presentations depending on the size of duplication were described: group I, <1.12 Mb, encompassing *YWHAE*; group II, >1.02 Mb, encompassing *YWHAE* and *HIC1* with or without *LIS1*; and group III, encompassing *LIS1* (9). The mutation reported here is compatible with group I (692.7 kb) previously associated with marfanoid habitus, cognitive dysfunctions, and autistic features. The dup17p13.3 can result in cardiac malformations (10), which were not present in our patient. We further hypothesized that the *YWHAE* gene, encoding the 14-3-3-epsilon protein, could be responsible for the cognitive and behavioral expression. Single nucleotide polymorphisms in the *YWHAE* gene

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Table 1. Clinical and Neuropsychological Assessment Data

Assessment	Results Before Treatment	Significance	After Personalized Care
Clinical Assessment			
Schizophrenic scales			
Positive and Negative Syndrome Scale	Total score = 69	[a]	Score = 47; improvement 32%[b]
Brief Psychiatric Rating Scale	Total score = 58	[a]	Score = 33; improvement 40%[b]
Scale for the Assessment of Thought, Language and Communication	Total score = 31		Score = 14; improvement 55%[b]
ADHD scales			
Conners' Adult ADHD Diagnostic Interview for DSM-IV	Inattentive symptoms without hyperactive symptoms	[a]	
Conners Scale (ADHD diagnostic scale)	Score = 30 (I: 20; H: 10)	[a]	Score = 13 (I: 9; H: 4)[b]
Developmental scales			
Autism Asperger assessment	Autism quotient = 24	[a]	NA
	Empathy quotient = 35		NA
Autism Diagnostic Interview	No autism spectrum disorder		NA
Neurologic soft signs (12)	Score = 16.5	[a]	NA
Minor physical abnormalities; adapted from Waldrop scale	7	[a]	NA
Neuropsychological Assessment			
Intellectual ability			
Block design (WAIS III)	Normalized score = 6	−1.3 SD[c]	−1 SD
Matrix reasoning (WAIS III)	Normalized score = 10	0 SD	−.3 SD
Similarities (WAIS III)	Normalized score = 12	+.7 SD	+1.7 SD
Processing speed			
Code (WAIS III)	Normalized score = 1	−4 SD[a]	−1.7 SD[c]
Selective attention			
D2 Test of Attention, concentration index KL	Normalized score = 83	pc 5[a]	pc 18[b]
Short-term memory/working memory			
Verbal: Digit span (WAIS III)	Normalized score = 6 − (F: 6; B: 5)	−1.3 SD[c]	−.3 SD
Visual: Spatial memory (WMS-III)	Normalized score = 7 − (F: 6; B: 6)	+1 SD	+1 SD
Verbal episodic memory (long-term)			
Free recall—Grober and Buschke	FR1: 8; FR2: 10; FR3: 11; delayed FR: 14	−1.4 SD[c]	+.5 SD[b]
Cued recall—Grober and Buschke	CR1: 15; CR2: 16; CR3:16; delayed CR: 16	pc 50	pc 56
Executive functions			
Planning: Zoo Map test	Profile score: 2	[a]	[c]
Flexibility: Trail Making Test A/B	A: 33 sec B: 157 sec	−1.5 SD[c] −8.5 SD[a]	−3.4 SD[a] −4.4[a,b]
Inhibition: Stroop	Interference−Naming score: 80 sec	−5.2 SD[a]	−4.4 SD[a,b]
Instrumental function			
Language	No alteration except for writing irregular words		
Calculation	Calculation alteration evolving since childhood	[a]	Improvement[b]
Praxis	Coordination difficulties and for motor praxis execution/lateralization difficulties/digital agnosia, without functional impairment	[a]	No improvement
Social cognition			
Theory of mind (Faux Pas Test below remediation) and MASC test (after remediation)	Total score: 29	−2.4 SD[a]	+1 SD[b]

ADHD, attention-deficit/hyperactivity disorder; B, backward; CR, cued recall; F, forward; FR, free recall; H, hyperactivity; I, inattention; KL, attention score (which is calculated from the number of d's crossed out correctly minus the number of letters crossed out incorrectly); MASC, Movie for the Assessment of Social Cognition; NA, not available; pc, percentile; WAIS, Wechsler Adult Intelligence Scale; WMS-III, Wechsler Memory Scale, third edition.

[a]Score is pathological (Z score > -2 SD).

[b]Score has been significantly improved after the personalized care.

[c]Score is weakened (-1.65 SD $<$ Z score < -2 SD).

were associated with schizophrenia and neuropsychiatric conditions including executive and attentional disturbances (5). Reduction of 14-3-3-epsilon protein in *Ywhae* (+/−) mice was associated with deficit in working memory and anxiety-like behavior (11). This protein interacts with disc-1, previously implicated in schizophrenia (11). Here, in accordance with the influence of 14-3-3-epsilon proteins on tyrosine hydroxylase, we report for the first time that dup17p13.3 is associated with dopamine deficiency. Speculating that patients with dopamine deficiency could take advantage of medications that increase dopamine levels, a dopaminergic agonist was administered alone and resulted in partial improvement of psychotic symptoms. Combining dopaminergic medication together with personalized remediation strategies alleviated symptoms and cognitive dysfunctions, including cognitive disorganization and attentional deficit.

In addition to personalized therapeutic strategies and screening for comorbid disorders, identification of a CNV in a patient with psychiatric disorders decreases the feeling of guilt in the parents and allows genetic counseling for the patient and his or her family. Although no definitive conclusions can be drawn in a given case about causality of CNV or neurotransmitter alterations, molecular diagnosis should be encouraged in psychiatry as part of the goal of more personalized treatment. Atypical clinical features should prompt screening for genetic abnormalities. Detection of mutations with possible causal roles in schizophrenia and psychotic disorders may allow for disentangling their heterogeneity and may enhance the understanding of their pathophysiology.

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References

1. Kirov G, Rees E, Walters JTR, Escott-Price V, Georgieva L, Richards AL, *et al*. (2014): The penetrance of copy number variations for schizophrenia and developmental delay. Biol Psychiatry 75:378–385.
2. Girard SL, Gauthier J, Noreau A, Xiong L, Zhou S, Jouan L, *et al*. (2011): Increased exonic de novo mutation rate in individuals with schizophrenia. Nat Genet 43:860–863.
3. Vyas NS, Shamsi SA, Malhotra AK, Aitchison KJ, Kumari V (2012): Can genetics inform the management of cognitive deficits in schizophrenia? J Psychopharmacol 26:334–348.
4. Preisig M, Fenton BT, Matthey ML, Berney A, Ferrero F (1999): Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of the French version. Eur Arch Psychiatry Clin Neurosci 249(4):174–179.
5. Jacobsen KK, Kleppe R, Johansson S, Zayats T, Haavik J (2015): Epistatic and gene wide effects in YWHA and aromatic amino hydroxylase genes across ADHD and other common neuropsychiatric disorders: association with YWHAE. Am J Med Genet Part B: Neuropsychiatric Genetics 168(6):423–432.
6. Berg D, Holzmann C, Riess O (2003): 14-3-3 proteins in the nervous system. Nat Rev Neurosci 4:752–762.
7. Torrey EF, Davis JM (2012): Adjunct treatments for schizophrenia and bipolar disorder: What to try when you are out of ideas. Clin Schizophr Relat Psychoses 5:208–216.
8. Bruno DL, Anderlid B-M, Lindstrand A, van Ravenswaaij-Arts C, Ganesamoorthy D, Lundin J, *et al*. (2010): Further molecular and clinical delineation of co-locating 17p13.3 microdeletions and microduplications that show distinctive phenotypes. J Med Genet 47:299–311.
9. Curry CJ, Rosenfeld JA, Grant E, Gripp KW, Anderson C, Aylsworth AS, *et al*. (2013): The duplication 17p13.3 phenotype: Analysis of 21 families delineates developmental, behavioral and brain abnormalities, and rare variant phenotypes. Am J Med Genet A 161A: 1833–1852.
10. Ho ACC, Liu APY, Lun KS, Tang WF, Chan KYK, Lau EYT, *et al*. (2012): A newborn with a 790 kb chromosome 17p13.3 microduplication presenting with aortic stenosis, microcephaly and dysmorphic facial features—is cardiac assessment necessary for all patients with 17p13.3 microduplication? Eur J Med Genet 55: 758–762.
11. Ikeda M, Hikita T, Taya S, Uraguchi-Asaki J, Toyo-oka K, Wynshaw-Boris A, *et al*. (2008): Identification of YWHAE, a gene encoding 14-3-3epsilon, as a possible susceptibility gene for schizophrenia. Hum Mol Genet 17:3212–3222.
12. Krebs MO, Gut-Fayand A, Bourdel M, Dischamp J, Olié J (2000): Validation and factorial structure of a standardized neurological examination assessing neurological soft signs in schizophrenia. Schizophr Res 45:245–260.