INTRODUCTION

22q11.2 Deletion Syndrome (22q11.2DS) is associated with a 20-fold higher risk of psychosis in lifespan compared to general population. Clozapine represents the gold standard for treatment-resistant schizophrenia (TRS), in 22q11.2DS as well. We report a not yet described gastroesophageal side effect of clozapine employment in 22q11.2DS and schizophrenia.

22q11.2 microdeletion syndrome (22q11.2DS) is caused by the microdeletion of the 11.2 strand in long arm of chromosome 22 and has an incidence spreading from 1:2,000 to 1:6,000 born alive, according to literature. 22q11.2DS is characterized by several clinical features involving congenital cardiologyc and pharyngo-palatal malformations, facial dysmorphic features, hypoparathyroidism, and thymic hypoplasia. 2q11.2DS is associated with an incidence of 25%–33% of psychotic disorders in lifespan sharing the same clinical characteristics with idiopathic psychosis in regard to premorbid conditions, age of onset, and symptoms. 4,5 Psychosis in 22q11.2DS is treated in the same way as idiopathic schizophrenia, and clozapine results the most effective tool in pharmacological treatment of treatment-resistant schizophrenia (TRS) in 22q11.2DS even if entailing more severe side effects, as seizures, hematological problems, and myocarditis, compared to individuals with nongenetic determined psychotic disorders. 6-8 The correlation between the employment of clozapine and the onset or worsening of obsessive-compulsive symptoms has been deeply investigated in literature. 9,10 The present work is aimed to further describe the set of side effects associated with the employment of clozapine in people with 22q11.2DS and schizophrenia. Our aim is to emphasize the efficacy of clozapine in TRS, encouraging its rechallenge with a tight monitoring after the resolution of potential severe side effects in order to manage such a critical clinical condition, as it has already been described in certain cases. 11 We are illustrating the case of a young girl with 22q11.2DS suffering from schizophrenia who developed a gastroesophageal side effect after clozapine introduction involving esophageal rumination, self-induced regurgitation, and caffean vomiting episodes.
2 MATERIALS AND METHODS

The patient was enrolled in October 2017 at the Outpatient Clinic for 22q11.2DS of Policlinico Umberto I of Sapienza University of Rome. Her parents signed free, informed consent. The patient, at the age of majority, signed a new informed consent. The current report adopted the Principles of Human Rights, as issued by the World Medical Association at the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequently amended by the 64th WMA General Assembly, Fortaleza, Brazil, in October 2013. Patient eligibility and diagnosis of psychotic disorder were based on the Structured Clinical Interview for DSM-IV Axis I Disorders / Patient Edition (SCID-I /P). Psychotic symptomatology was assessed with the Positive And Negative Syndrome Scale (PANSS).12

2.1 Description

The present description refers about a young girl who has been diagnosed with 22q11.2DS in November 2017 by Microarray-based Comparative Genomic Hybridization (aCGH). The patient has undergone several clinical and genetic studies, which have excluded other conditions apart from the 22q11.2DS. The patient, who currently is 19 years old, came at our service in October 2017 due to a symptomatology characterized by psychomotor agitation, restlessness, behavior and thought disorganization, insomnia, and hyperphagia. First psychiatric symptoms appeared at the age of 11, involving phobias and bizarre hypochondriac fears in addition to progressive isolation and relational withdrawal. During the following years, a sudden and progressive cognitive decline appeared with an almost total impairment of patient's executive functions, compromising academic performance, verbal abilities, reading and writing functions, and relational skills. Different neuropsychiatric symptoms furtherly occurred, as outbursts and aggressive behaviors, psychogenic dysphonia (as evidenced by an ENT consult which excluded organic etiology), social-functioning progressive impairment, and negative symptoms; several psychotrophic treatments have then been employed, following one another with low benefit: quetiapine extended release (ER) (up to 200 mg/die), risperidone (up to 2.5 mg/die), aripiprazole (up to 15 mg/die), clomipramine (up to 30 mg/die and then suspended after iatrogenic psychomotor activation), mirtazapine (up to 15 mg/die), and valproate (up to 200 mg/die). Finally, clozapine was introduced with progressive dosage up to 200 mg/die, leading to a cognitive and relational improvement, as well as a significant reduction of insomnia. However, disorganized behavior persisted without any significant improvement in compulsions regarding sweet food craving. Thought was persistently poor and concrete. In November 2018, the patient had a seizure and electroencephalogram (EEG) showed rare and short sequences of slow waves. Clozapine dosage has been then reduced to 125 mg/die. At that time, the patient showed gastroesophageal ruminating avoiding solid food: Omeprazole (40 mg/die) was prescribed. Since February 2019, gastroesophageal symptoms worsened and episodes of caffean vomiting were reported, requiring a hospitalization in April 2019: An esophagogastroduodenoscopy (EGDS) revealed nonbleeding erosions, hyperemia, and edema of the distal esophagus, establishing the diagnosis of reflux esophagitis. In the following months, the patient did not show further outbursts or violent behaviors but flattened affect, social withdrawal, and relational isolation persisted despite the pharmacological treatment. Clozapine has been suspected to be responsible of gastroesophageal symptoms and progressively reduced up to suspension. A progressive worsening of clinical conditions was then observed with outbursts and aggressive episodes reappeared. Quetiapine ER 800 mg/die, gabapentin 1200 mg/die, mirtazapine 30 mg/die, and cariprazine 1.5 mg/die were prescribed, and gastrointestinal ruminating significantly improved without any new vomit episodes. Esophagitis and esophageal erosions improved as revealed by a EGDS in August 2019. However, psychomotor activation, outbursts, and violent behaviors persisted and auditory hallucinations with ideo-affective dissociation appeared. Quetiapine ER was then reduced up to 300 mg/die, mirtazapine was suspended, and a new employment of clozapine was challenged with a very slow titration up to 125 mg/die in a month lapse: Relational skills and interpersonal functioning improved and aggressive behaviors were managed. Negative symptoms persisted. Clozapine was augmented up to 175 mg/die, and quetiapine ER was reduced to 200 mg/die. In October 2019, a new EEG did not show significant abnormalities. In December 2019, a bacterial cystitis was treated with antibiotics and subsequently compulsive symptoms appeared, with repetitive urination attempts without real need. These compulsions lasted several months after the infection resolution confirmed by laboratory analysis. In January 2020, quetiapine ER was gradually suspended and clozapine was augmented up to 200 mg/die: Compulsive ruminating and self-induced esophageal regurgitation reappeared. A fluvoxamine treatment was attempted up to 75 mg/die to deal with compulsive symptoms and increase blood level of clozapine.13 Despite negative symptoms and compulsive food seeking persisted, the patient showed a global improvement in her clinical status, besides the attenuation of gastroesophageal ruminating: Aggressive and disorganized behaviors were successfully managed. Other symptoms such as psychomotor activation, and auditory hallucinations with ideo-affective dissociation, did not appear anymore.
To our knowledge, this is the first report of compulsive gastroesophageal rumination as a side effect of clozapine's employment for psychosis treatment in 22q11.2DS. We sought to describe mutual interaction between obsessive-compulsive symptoms induced by clozapine and its complex peripheral pharmacodynamic properties. Clozapine represents the gold standard for treatment-resistant schizophrenia (TRS), both in idiopathic schizophrenia and in 22q11.2DS. We confirmed the efficacy of clozapine in treatment of psychotic symptoms, behavioral disorders, and cognitive deficits in TRS conditions. Indeed, several antipsychotic strategies have failed in treating the patient's psychotic symptoms which further worsened at time of clozapine's suspension, as well as confirmed in literature. Although at a lower level, clozapine improved patient's negative and cognitive symptoms as well; the patient showed discrete relational skills with better interpersonal functioning, partially recovering some cognitive abilities as drawing and writing. A significant improvement in psychopathological conditions appeared on one side, along with the emergence of an uncomfortable side effect on the other one, with real-life functioning impairment. Interestingly, a dose-dependent correlation between clozapine and compulsive symptoms was established: esophageal compulsive rumination and self-induced regurgitation caused histopathologic damages of esophageal mucosa determining several caffean vomiting episodes. We suggest a tight correlation between clozapine-induced compulsive symptoms and pharmacodynamic effects on gastroenteric system, as corroborated ex adiuvantibus by the prompt improvement of esophageal lesions at the time of clozapine suspension. Considering the report of serious episodes of acute esophageal necrosis with clozapine employment, we hypothesize that gastroesophageal symptoms may have been caused by the overlapping of clozapine-induced rumination with a direct damage that this antipsychotic might have caused on esophageal mucosa by the means of peripheral pharmacodynamic effects. We strongly believe that further investigations in this direction are required.

In conclusion, we believe that this clinical report contributes to demonstrate that although the treatment of TRS with clozapine in 22q11DS may be complicated by several additional medical conditions, a rechallenge with clozapine after the resolution of its potential severe side effects such as gastroesophageal rumination should continue to be encouraged with intensive monitoring.

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
Tommaso Accinni, Marianna Frascarelli, and Fabio Di Fabio: wrote the clinical report and treated the patient. Martina Fanella and Carlo Di Bonaventura: collected the medical data and treated the patient. Francesco Ghezzi, Alessia Panzer, and Antonino Buzzanca: collected the medical data and critically revised the manuscript. Luca Carlone and Nicoletta Girardi: involved in drafting the manuscript and helped in acquisition of data. Massimo Pasquini and Fabio Di Fabio: conceived the publication and revised the manuscript. All authors listed gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

ETHICAL APPROVAL
The present study conforms to Declaration of Helsinki. Patient signed a written consent.

DATA AVAILABILITY STATEMENT
Data supporting the findings of this study are available from the corresponding author M. F. on request.

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REFERENCES
1. McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. Nat Rev Dis Prim. 2015;19:1-15071.
2. Botto LD, May K, Fernhoff PM, et al. A population-based study of the 22q11.2 Deletion: Phenotype, incidence, and contribution to major birth defects in the population. Pediatrics. 2003;112:101-107.
3. Murphy KC. Schizophrenia and velo-cardio-facial syndrome. Lancet. 2002;359:426-430.
4. Verhoeven WMA, Egger JIM. Atypical antipsychotics and relapsing psychoses in 22q11.2 deletion syndrome: A long-term evaluation of 28 patients. Pharmacopsychiatry. 2015;48:104-110.
5. Siskind D, Siskind V, Kisely S. Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. Can J Psychiatry. 2017;62:772-777.
6. Gladston S, Clarke DJ. Clozapine treatment of psychosis associated with velo-cardio-facial syndrome: benefits and risks. J Intellect Disabil Res. 2005;49:567-570.
7. Ruhe AM, Qureshi I, Procaccini D. Clozapine-induced myocarditis in an adolescent male with DiGeorge Syndrome. Ment Heal Clin. 2018;8:313-316.
8. Fanella M, Frascarelli M, Lambiase C, et al. Myoclonic epilepsy, parkinsonism, schizophrenia and left-handedness as common neuropsychiatric features in 22q11.2 deletion syndrome. J Med Genet. 2020;57:151-159.
9. Scheltema Beduin AA, Swets M, Machielsen M, et al. Obsessive-compulsive symptoms in patients with schizophrenia: a naturalistic cross-sectional study comparing treatment with clozapine,
olanzapine, risperidone, and no antipsychotics in 543 patients. J Clin Psychiatry. 2012;73:1395-1402.

10. Kim DD, Barr AM, Lu C, et al. Clozapine-associated obsessive-compulsive symptoms and their management: A systematic review and analysis of 107 reported cases. Psychother Psychosomat. 2020;89:151-160.

11. Butcher NJ, Fung WLA, Fitzpatrick L, et al. Response to clozapine in a clinically identifiable subtype of schizophrenia. Br J Psychiatry. 2015;206:484-276.

12. Lu ML, Chen TT, Kuo PH, Hsu CC, Chen C. H. Effects of adjunctive fluvoxamine on metabolic parameters and psychopathology in clozapine-treated patients with schizophrenia: A 12-week, randomized, double-blind, placebo-controlled study. Schizophr Res. 2018;193:126-133.

13. Kane JM, Agid O, Baldwin ML, et al. Clinical guidance on the identification and management of treatment-resistant schizophrenia. J Clin Psychiatry. 2019;80(2):18com12123.

14. Tollefson GD, Dellva MA, Mattler CA, et al. Controlled, double-blind investigation of the clozapine discontinuation symptoms with conversion to either olanzapine or placebo. The Collaborative Crossover Study Group. J Clin Psychopharmacol. 1999;19:435-443.

15. Moncrieff J. Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. Acta Psychiatr Scand. 2006;114:3-13.

16. Goudie AJ, Cole JC. Switching antipsychotics. Antipsychotic tolerance, withdrawal and relapse: Unresolved issues and research implications. J Psychopharmacol. 2008;22:815-817.

17. Pautola L, Hakala T. Medication-induced acute esophageal necrosis: a case report. J Med Case Rep. 2016;10:267.

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