Metyrosine treatment in a woman with chromosome 22q11.2 deletion syndrome and psychosis: a case study

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Background: People with 22q11.2 deletion syndrome (DS) are assumed to be especially vulnerable to developing mental illness such as psychosis.
Aim: The study was established to contribute to knowledge about metyrosine medication in patients with 22q11.2 DS and psychosis.
Methods: A case study was established including a woman with intellectual disability, 22q11.2 DS, and psychosis. Metyrosine medication was implemented, as conventional anti-psychotic medication was unsuccessful.
Results: Effect of metyrosine medication included both psychotic symptom relief with decreased aggressive behaviour. Adjunctive milieu therapy contributed to complience.
Conclusion: For patients with 22q11.2 DS and psychosis, metyrosine medication may prove effective. However, there are significant ethical dilemmas related to metyrosine medication for psychotic symptoms.

Keywords 22q11.2 deletion Syndrome, intellectual disability, psychosis, psychotropic medication

Introduction

The chromosome 22q11.2 deletion syndrome (22q11.2 DS), also called DiGeorge syndrome or Velocardiofacial syndrome (VCFS), is a multiple anomaly disorder that is caused by a microdeletion of DNA. The 22q11.2 DS is more common than earlier studies indicate. A study of prenatal samples indicates a frequency of about 1 in 1000 (Grati *et al*. 2015). A number of medical and emotional conditions are associated with 22q11.2 DS, such as cardiovascular malformations, palatal abnormalities, facial dysmorphic features, immune deficiency, urogenital disorders, and mental illness (McDonald-McGinn *et al*. 2016, Schneider *et al*. 2014, Young *et al*. 2011). Cognitive impairments affect most people with 22q11.2 DS, including impaired attention, working memory, executive functions, and verbal learning (Young *et al*. 2011). Mean IQ is found to be about 70 and severe and profound ID is uncommon (McDonald-McGinn *et al*. 2016). Both behavior and social functioning may be affected negatively (Kates *et al*. 2015). An extremely high frequency of psychosis is found in patients with 22q11.2 DS (Monks *et al*. 2014, Schneider *et al*. 2014). A multi-site study including about 1400 persons with 22q11.2 DS aged 6-70 found psychotic disorders in 41% from age 25 (Schneider *et al*. 2014).

Recommended treatment for psychosis is a combination of medication and a broad range of psychosocial treatments and follow-up (van Os and Kapur 2009). Psychotropic medication may help people with 22Q11.2 DS who develop psychosis (Dori *et al*. 2017, Schneider *et al*. 2014). For example Verhoeven and Egger (2015) found clozapine, quetiapine, and valproic acid to be effective. However, Boot *et al*. (2015) discredit the conclusions of Verhoeven and Egger and argue for 'standard pharmacological treatment of psychotic illness in 22q11.2 DS.' A recent case report where clozapine (a standard second-choice antipsychotic) was not effective illustrates the difficulties associated with medication (Angelopoulos *et al*. 2017). Regarding side effects, people with 22Q11.2 DS are found to suffer from the same side effects as patients in the general population (Dori *et al*. 2017). However, according to the vascular deficits related to the 22Q11.2 DS, metabolic and cardiovascular levels should be carefully monitored in people with 22Q11.2 DS who use anti-psychotic medication (Dori *et al*. 2017).

Metyrosine is mainly indicated in the surgery of patients with pheochromocytoma, a catecholamine-secreting tumor (Perry *et al*. 1990). Methyrosine inhibits

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tyrosine hydroxylase, which catalyzes the first transformation in catecholamine biosynthesis, thereby lowering the levels of catecholamine. However, metyrosine has also been used in neurotypical patients with depressive disorder and obsessive-compulsive disorder (Carandang and Scholten 2007). Metyrosine is used, but presumably rarely, to reduce symptoms of psychosis in people with 22q11.2 DS who have responded inadequately to conventional anti-psychotic treatment (Carandang and Scholten 2007, Graf *et al*. 2001). Since there are no studies of long-term effects in humans or in animals, metyrosine should be used with caution in patients with impaired hepatic or renal function (Aton Pharma, Patient Information Leaflet).

The chromosomal region including the gene encoding catechol-*O*-methyltransferase (COMT) is affected in people with 22q11.2 DS. COMT is one of the enzymes that metabolize catecholamine such as dopamine (Grossman *et al*. 1992). This loss of one copy of the COMT gene causes disturbance in regulation of COMT in the brain. The regions of the brain where the presynaptic dopamine transporter expression is low, such as the prefrontal cortex, are particularly affected (Matsumoto *et al*. 2003). This may be one of the reasons why people with 22q11.2 DS have increased risk of behavioral problems and mental illness. There are three different modalities of COMT enzyme activity: high activity in the Val/Val genotype, intermediate activity in the Val/Met genotype, and low activity in the Met/Met genotype (Hosák 2007). Patients with the Met158 allele of the COMT gene have increased risk of aggressive and violent behavior in schizophrenia (Bhakta *et al*. 2012). Decomposition of catecholamine is reduced in patients with Val108/158Met or 158 Met/158Met, which may be equated with lacking one allele of the COMT gene in 22q11.2 DS.

Aim

In the present article, we address the use of metyrosine in an adult woman with 22q11.2 DS and additional psychotic disorder.

Methods

Design

This is a case report. The design is entirely retrospective, as we only decided to report this case after we realized that metyrosine was more adequately effective for this patient than conventional antipsychotic medication.

Measures

The *Positive and Negative Syndrome Scale*, PANSS, was used to assess possible psychotic symptoms (Kay *et al*. 1987). The PANSS has three domains: positive symptoms, negative symptoms, and a general psychopathology subscale. The scoring values are 1–7. The *Aberrant behaviour Checklist*, ABC (Aman and Singh 1986), is a screening tool for behavior problems in persons with ID. The ABC was used to assess possible effects of medication. The ABC has 58 items with scoring values from 0 to 3. The items are summed up in five subscales: irritability, lethargy, stereotypy, hyperactivity, and inappropriate speech.

Procedure

A long-term psychiatric inpatient was studied, (period 2), in the setting of a specialized psychiatric inpatient unit (period 3) — see Table 1. The patient pathway through the psychiatric services covered more than five years and involved one outpatient unit and four different inpatient units. The patient was assessed for a syndrome, mental illness, and global functioning. A number of conventional and atypical antipsychotics were tried out, including clozapine, and different milieu-therapeutic regimes. The milieu therapy differed in the general inpatient unit (period 2) from the specialized unit (period 3). In the general unit, the patient was provided with basic nursing, including provision of medication and seclusion, when she showed aggressive behavior. In the specialized unit, the milieu therapy was adjusted to the patient's lack of communicative skills. The milieu therapy especially emphasizes facilitated nurse–patient communication and task sustenance, which have both proved to be effective in severely disturbed patients with psychosis and ID (Bakken *et al*. 2008). Non-verbal validation was emphasized (Bakken *et al*. 2017). In this paper, results from clinical observations, PANSS, and the ABC will be presented.

Ethical considerations

Permission to conduct the study was given by the following authorities: the director of the specialized psychiatric department and the hospital's Privacy Protection Supervisor. The patient was informed consecutively about medication regimes, and she did not at any point object. However, she was not considered to be able to consent because of her mental illness combined with cognitive impairments. The patient's parents gave their informed consent for participation.

Case presentation

Pre-morbid function

The patient is a woman in her late twenties. She grew up in a well-functioning family with married parents and two siblings. She was born with an open ventricular septal defect (VSD) that closed spontaneously. The patient had social and communication difficulties from childhood. She had subject-related difficulties at school, and also problems with maintaining friendships. However, she had an active life, practicing martial arts, playing an instrument, and participating in physical activities.

Presentation of symptoms and diagnostic conclusions

At age 19, the patient presented with severe fatigue and tiredness. A thorough assessment led to the conclusion that she had Graves' disease, which was treated with a

Table 1 Overview of treatment settings, medication, symptoms, and psychosocial interventions

Period	Duration	Treatment setting	Psychotropic medication	Symptoms	Psychosocial interventions
1	About 3 weeks About 3 years About 2 years	Acute inpatient. Ward outpatient treatment First episode inpatient	Olanzapine — weight gain, blood sugar, leucopenia. Hydroxyzine — unclear effect. Aripripazole — unclear effect. Amisulpride — no effect, severe side effects. Ziprasidone — no effect observed, Lamotrigine — No effect observed. Quetiapine — unclear effect, tiredness. Klorprodiksen — severe tiredness and passivity. Levopromazin — tiredness and salivation. Haloperidol — weight loss, compulsions. Klozapine — unclear effect, severe tremor, leucopenia. Oxazepam — no effect	**Debut:** global functioning fall****, delusions****, hallucinations****, Disorganization of talk and behavior***, fatigue****, social withdrawal****, anxiety****, aggression***	Outpatient: Lived with her parents. No mental health interventions. Inpatient. Milieu therapy. No individual or group therapy
2	About 2 years	Long term inpatient unit general	Risperidone 2.5 mg → 1.5 mg. **Trial 1**: metyrosine: initially 1500 mg/day → low BP → 750 mg. Unclear effect → discontinued after 9 months for one month **Trial 2:** metyrosine 750 mg → 500 mg	**Trial 1:** global functioning fall**, delusions?, hallucinations?, Disorganization of talk and behavior***, fatigue, social withdrawal***, anxiety***, aggression=***. **Cessation 1**: global functioning fall****, delusions ?, hallucinations ?, Disorganization of speech and behavior***, fatigue****, social withdrawal****, anxiety****, aggression****	Milieu therapy. Seclusion, *ad hoc*
3	14 months	Inpatient unit, specialized for adults with ID	Lithium 166 mg — unclear effect. Lamotrigin — unclear effect. Methyldopa 1250 mg (as substitute for metyrosine) — unclear effect. Risperidone: 1.5 mg adjunctive in trial 2, 3 and 4. **Trial 2**: metyrosine 500 mg: discontinued after 14 days for 3 months. **Trial 3:** metyrosine 6 months. Cessation for 1.5 months. **Trial 4**: metyrosine 750 mg — continued	**Trial 2**: as trial 1. **Cessation 2**: as break 1. **Trial 3:** global functioning fall***, delusions**, hallucinations**, Disorganization of talk and behavior **, fatigue **, social withdrawal****, anxiety**, aggression*. **Cessation 3**: as break 1. **Trial 4**: As trial 3	Adjusted milieu therapy in a specialized unit for patients with ID. Family sessions
4	About 3 years	Follow up by psych. outpatient unit	**Trial 4:** metyrosine 750 mg	**Symptom presentation two years after hospital discharge**: global functioning fall**, delusions**, hallucinations**, Disorganization of talk and behavior*, fatigue**, social withdrawal*, aggression*	Sheltered living in a group home with around the clock care

Symptoms: *=not observed, **=some/little symptom presentation, ***=moderate symptom presentation, ****=severe symptom presentation.

thyroid resection. The onset of psychotic symptoms occurred concurrently. Somatic symptoms led to neurological assessment. 22q11.2 DS syndrome was suspected and confirmed by genetic testing. The patient presented with the following symptoms during the first episode (debut): severe fall in global functioning, paranoid and bizarre delusions-especially concerning her own body and ideas about motherhood and childbirth, and auditory and somatosensory hallucinations (frequently reporting that she could feel a baby inside and that she was about to give birth). An overview of symptoms during the four periods is presented in Table 1.

The patient's auditory hallucinations included voices commenting and saying negative things about her. She displayed severe speech disorganization, including incoherent speech, derailment and loss of verbal speech, disorganized behavior and negative symptoms including lack of motivation, severe fatigue, and social withdrawal. The patient showed affective symptoms with several daily mood swings from elevation to crying, sadness, and complete apathy. She additionally displayed severe anxiety and restlessness. Concurrently, with a high psychotic and affective symptom load, the patient showed severe aggression towards people and objects. Verbal outbursts included threats of violence. Physical outbursts included throwing and breaking objects, and self-harm such as head banging or hitting herself. The patient was diagnosed as having a schizoaffective disorder according to ICD 10 criteria, in addition to 22q11.2 DS and Grave's disease. We still do not know which variant the patient has of the one gene coding for the COMT enzyme.

Medication, psychosocial interventions, and treatment settings

Conventional antipsychotics were tried out during outpatient and inpatient treatment for approximately five–six years (period 1, 2, and 3). The effects of conventional antipsychotics were typically unclear, transient, and limited, while the side effects were frequent, and in some situations, disabling. The severity of the symptoms and difficulty of finding adequate antipsychotic treatment resulted in continual hospitalization in closed wards for four years. The patient was first treated in two different general psychiatric units (period 1 and 2), before she was transferred to a specialized psychiatric inpatient unit for adults with intellectual disabilities (period 3).

Metyrosine was introduced for the patient and discontinued three times: once deliberately as part of efficacy assessment and twice due to problems with supplies of metyrosine. After two to three days, an increase in delusions, hallucinations, disorganization, and aggression was observed, as described above, at each metyrosine cessation. With regard to other psychotropic medications, these were not eliminated because of the very high symptom load.

First metyrosine trial: 9 months. Monotherapy. Some improvements in dysfunctional affect regulation were observed. As there was no effect on daily and social functioning or hypotension and tiredness at the highest dose (1500 mg daily), the medication was first reduced to 250 mg × 3, and then discontinued due to psychotic residual symptoms.

First cessation: 4 weeks for effect assessment.

Second metyrosine trial: 4 months. Risperidone 1 mg + 1.5 mg adjunctive because of residual psychotic symptoms with metyrosine as monotherapy. When it was reduced to 250 mg × 2 the last month because of delivery problems, the patient still showed effects. Metyrosine was discontinued due to delivery problems 14 days after admission to the specialized inpatient unit.

Second cessation: 3 months due to delivery problems. Severe deterioration was observed, with more severe aggression. Treatment trials with lithium, lamotrigine, and methyldopa were given without success.

Third metyrosine trial: 6 months. Metyrosine 250 mg × 3 (firstly metyrosine 250 mg × 4, which elicited hypotension) + risperidone 1.5 mg adjunctive (the patient showed drooling on risperidone 2.5 mg). Significant improvement on emotion regulation and social and daily function was observed.

Third cessation: 1.5 months due to delivery problems.

Fourth metyrosine trial: Metyrosine 250 mg × 3 reintroduced with risperidone 1.5 mg as adjunctive medication. This combination has been continued since.

Psychosocial interventions were not offered during outpatient treatment. During the last inpatient stay (period 3), adjusted milieu therapy (see *Procedure*) and family sessions were conducted.

Results

The PANSS scores presented in Table 2 are mean and mode scores before and after metyrosine medication was administered in adequate dosages in the specialized psychiatric inpatient unit (period 4). The PANSS scores in the specialized unit improved for the three sub-scales. The results from the ABC scores are presented in Table 3.

The results from the ABC scores showed that the three times metyrosine was discontinued, aggression then increased after a few days. The last time metyrosine was reintroduced, it was evident that metyrosine reduced mood cycling, psychotic symptoms, and aggressive outbursts, thus making the patient accessible to psychosocial interventions, mostly milieu therapy.

Discussion

Metyrosine combined with risperidone and adjusted milieu therapy relieved psychotic symptoms and reduced aggressive behavior. For the patient concerned, the metyrosine medication positively impacted delusions, hallucinations and disorganized behavior by decreasing the symptom

Table 2 The PANSS scores before and after metyrosine medication in the specialized unit

PANSS		Mode score		Mean score	
		Before	After	Before	After
Positive symptom scale	1. Delusions	5	3	4.8	3.3
	3. Hallucinations	4	3	3.7	3.4
	4. Hyperactivity	5	3	5.2	3.3
	7. Hostility	5	3	5.1	3.4
Negative symptom scale	2. Emotional withdrawal	4	3	4.2	2.9
	4. Passive/apathetic social withdrawal	4	3	4.0	2.9
General psychopathology scale	5. Mannerisms and posturing	4	3	3.8	3.2
	7. Motor retardation	4	3	4.3	3.0
	14. Poor impulse control	6	3	5.8	2.9
	16. Active social avoidance	3	2	3.4	2.4

burden. As verbal speech had disappeared in the acute phases,

Content of delusions had been hard to interpret. When the patient regained her verbal speech ability, the tentative diagnosis of a condition in the schizophrenic spectrum was confirmed (Hurley 1996, Bakken *et al*. 2007). Beside decreased disorganization, the effect observed in the specialized unit was for the most part associated with a reduction in aggressive behavior. This effect was seen after a few days, and both physical and verbal aggression were reduced.

A metyrosine dosage of 250 mg × 3 is low. However, this low dosage was necessary because of hypotension on a higher dosage. At the same time, 750 mg had about the same effect as 1500 mg.

Additionally, patients with cognitive impairments may not report side effects (Tveter *et al*. 2014). With metyrosine medication, inpatient hospitalization is necessary for both initiating and adjusting the dosage because of possible side effects such as sedation, extrapyramidal signs (EPS), diarrhea, hypotension, and mental disturbances such as frightening dreams, anxiety, and disorientation (Perry *et al*. 1990). Adverse effects were therefore thoroughly observed in this case. The blood pressure was monitored closely.

Prior to metyrosine medication, the patient's affect regulation was severely dysfunctional, so that even experienced milieu therapists in the specialized inpatient unit were unable to calm the patient down during temper tantrums. After medication, the patient achieved more stable affect regulation. Staff members were then able to provide communication with low expressed emotion (Bakken *et al*. 2008, McFarlane *et al*. 2003).

There are a number of ethical considerations related to this case, especially patient participation, possible side effects, and the costs. There is a lack of research encompassing long-term effects and side effects (Lin *et al.* 2009). Consent by proxy-given by the parents in this case-implies that the patient may be exposed to unknown long-term side effects. Because of the cost of medication (about Euro 200,000 annually), this case was raised for discussion in the university hospital clinical ethics committee. The committee concluded that these costs were justified by significant improvement in the patient's daily functioning and the fact that without metyrosine medication, staff expenses in community care would exceed medication costs. The patient was informed of this research study, and did not have any objections to it.

The patient has now lived in a sheltered community residence for more than three years and her parents underpin that she expresses contentment with her life. She is followed up by an out-patient team comprising a psychiatrist, an endocrinologist, and her general practitioner. She continues to express delusions and mood swings, but they are much less strong and frightening. Delusions about motherhood have disappeared. She has regained verbal language, she socializes with family and carers, and

Table 3 The ABC scores with and without metyrosine medication in the specialized unit

ABC	Scores 2. trial At arrival Specialized inpatient unit	Scores 2. break A	Scores 2. break B	Scores 3. trial	Scores 3. break	Scores 4. trial	Max. score	90 percentile
Irritability 15 items	39	**39***	**40**	13	**38**	16	***45***	***21***
Lethargy 16 items	33	**35**	**36**	9	**35**	11	***48***	***15***
Stereotypy7 items	0	**4**	**4**	2	**4**	2	***21***	***5***
Hyperactivity16 items	25	**28**	**27**	14	**27**	16	***48***	***17***
Inappr. speech 4 items	4	**7**	**7**	3	**6**	2	***12***	***5***

*bold scores=metyrosine discontinued.
The italic values indicate max score and the 90 percentile scores, respectively.

expresses verbally that she enjoys the company of other people. She does not display anxiety attacks, aggression, disorganized behavior or severe passivity.

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Contributors

MHE and TLB conceived and designed the study, obtained funded and ethics approval, analyzed the data, wrote the article in whole/part, and revised the article. MHE, IHH, and ANK collected and analyzed the data.

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