22q11 Deletion syndrome and neurotransmitter systems in unchallenged and challenged conditions
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CHAPTER 2

Disrupted dopaminergic neurotransmission in 22q11 deletion syndrome

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ABSTRACT
22q11 Deletion syndrome (22q11DS) is associated with chromosome 22q11 microdeletions and high rates of psychiatric disorders. Susceptibility for these disorders could be explained by haploinsufficiency of the catechol-O-methyltransferase (COMT) gene, which encodes an enzyme involved in dopamine (DA) breakdown. It is unknown how dopaminergic neurotransmission is affected in people with 22q11DS. To date, there have been no controlled studies investigating dopaminergic neurotransmission in people with 22q11DS. We report the results of a challenge study in high-functioning adults with 22q11DS and age- and gender-matched controls using neuro-endocrine and peripheral dopaminergic markers. At baseline, 22q11DS subjects compared to controls had higher urine DA levels and lower plasma levels of the predominant DA metabolite homovanillic acid (HVA). Following DA depletion, 22q11DS subjects showed lower urine and plasma HVA levels and a lower prolactin response than controls. The ratio of DA/HVA, a rough index of DA turnover, was significantly higher in the 22q11DS subjects at baseline and after DA depletion. Our results suggest that adults with 22q11DS have disrupted dopaminergic neurotransmission, which might explain their susceptibility for psychiatric disorders.
INTRODUCTION

22q11 Deletion syndrome (22q11DS) or velo-cardio-facial syndrome (VCFS) is caused by a microdeletion on the long arm of chromosome 22 and occurs in approximately 1 out of every 4000-5000 live births [31,34]. The syndrome is associated with multiple congenital malformations and cognitive deficits [14,21]. In addition, people with 22q11DS are at increased risk of developing psychiatric disorders including schizophrenia-like psychosis, attention deficit hyperactivity disorder and anxiety disorders [4,12,17,28,29].

Among the genes in the deleted region, the catechol-O-methyltransferase (COMT) gene has been of particular relevance for psychiatric research [35,39]. Subjects with 22q11DS carry only one copy of this gene. It encodes an enzyme that is important for the breakdown of catecholamines, including dopamine (DA) and norepinephrine (NE). The gene is expressed in all regions of the human central nervous system, but the enzyme is particularly important for DA clearance in the prefrontal cortex (PFC) [39]. COMT contains a functional polymorphism (Val^108/158Met) with concomitant high- and low-activity variants of the enzyme [7]. The activity of the Met allele (Met/Met homozygotes) in PFC in postmortem human subjects is found to be about 40% lower than the activity of the Val allele (Val/Val genotype) [7]. Haploinsufficiency of COMT is hypothesized to result in low enzymatic activity and consequently high DA levels [9,11,16,18]. Dopaminergic dysfunction plays a major role in the pathophysiology of psychosis, and other psychiatric disorders that frequently occur in people with 22q11DS [2,6,36]. High DA levels, in PFC as well as other brain areas, could explain the increased risk for neuropsychiatric disorders in 22q11DS [9,39].

Outcome measures to assess dopaminergic neurotransmission include the neuro-endocrine response of the hormone prolactin (PRL) [32] and peripheral values of DA, NE, and their metabolites [25]. The cells of the anterior pituitary (lactotrophs) which synthesize and secrete PRL have spontaneously high secretory activity [13]. DA is the predominant hypothalamic inhibiting factor of PRL release in humans, and DA D2 receptor stimulation has inhibiting effects on PRL gene transcription, synthesis and release in the anterior pituitary [19].

In addition, in psychiatric research, pharmacological challenge tests have been used to discover abnormalities in the dopaminergic system, for example with α-methyl-para-tyrosine (AMPT). AMPT is a reversible inhibitor of the first and rate-limiting reaction in catecholaminergic biosynthesis, the hydroxylation of tyrosine to form 3,4-dihydroxyphenylalanine (dopa) [10]. Only one small study in subjects with 22q11DS focused on effects of AMPT [18]. In an uncontrolled, open label trial, four 22q11DS subjects with neuropsychiatric or behavioral dysfunction were administered prolonged and relatively low-doses of AMPT in addition to their existing medication. No conclusions can be drawn from their measurements of catecholamines and metabolites. Owing to beneficial effects, three out of four patients continued with AMPT after the trial.
To date no controlled study has yet reported on how dopaminergic neurotransmission is affected in people with 22q11DS and how this may contribute to their increased risk for developing psychopathology.

The purpose of this study was to determine whether neuro-endocrine, and peripheral dopaminergic markers, both at baseline and following an acute dopaminergic depletion challenge, were different in healthy, high-functioning adults with 22q11DS compared to healthy controls. Plasma PRL levels and plasma and/or urine levels of DA and NE and their metabolites were used as outcome measures. We hypothesized that due to COMT haploinsufficiency people with 22q11DS have compromised dopaminergic neurotransmission. We hypothesized both at baseline and following DA depletion: (1) lower PRL levels in 22q11DS subjects; (2) higher levels of DA and lower levels of dopaminergic metabolites in 22q11DS subjects; (3) no difference in levels of NE and its metabolites, as the primary pathway of NE metabolism involves deamination by monoamine oxidase [30].

MATERIALS AND METHODS

Subjects
The participants were 12 neuroleptic and psychostimulant-naive adults with 22q11DS (five males and seven females) and 12 age- and sex- matched healthy controls, aged 18-39 years. Full scale intelligence (mean ± SD) was determined using a shortened version of Wechsler Adult Intelligence Scale – III in subjects with 22q11DS (79.8 ± 9.3, n = 12). Subjects with 22q11DS were recruited through the Dutch 22q11DS family association and through the departments of three Dutch Clinical Genetics Centers. Control subjects were recruited from the Academic Medical Center. Inclusion criteria for all subjects were as follows: (1) no current or past psychiatric history, (2) no current or previous exposure to anti-psychotic or stimulant medication; (3) no lifetime history of alcohol or substance abuse or dependence; (4) no concomitant or past severe medical conditions; (5) no pregnancy; (6) a deletion on 22q11 as determined by fluorescent in-situ hybridisation (22q11DS subjects). Each participant gave written informed consent after explaining the full study procedure. The protocol was approved by the Ethics Committee of the Academic Medical Center of Amsterdam.

Depletion Regimen
The doses and frequency of AMPT administration (500 mg three times over 4 h) were selected to provide and maintain significant inhibition of tyrosine hydroxylase activity. These doses were lower compared to several other recent dopaminergic depletion studies [3,24,42]. AMPT was given for this short period, based on the expectation that this duration of treatment would be adequate to induce marked DA depletion. The first AMPT dose was given in the morning (1000 h = T0) after baseline blood samples were taken. Subsequently, 500 mg AMPT was administered at 1200 h (T2) and at 1400 (T4). To prevent the formation of AMPT crystals in the urine, subjects were instructed to drink plenty of
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fluids [42]. Through plasma AMPT levels were measured at T3 and T6 by using gas chromatography/mass spectrometry. Inter- and intra-assay coefficient of variation was less than 5% for all assays.

Catecholamine Metabolites and Prolactin

Subjects presented at 0930 h were cannulated in a forearm vein. Blood samples were drawn at T0, T3, and T6 for determination of plasma levels of PRL, homovanillic acid (HVA), vanillylmandelic acid (VMA) and 3-methoxy-4-hydroxy-phenylglycol (MHPG). Urine samples were collected at T0 and T6 for determination of DA, epinephrine, NE, HVA, VMA, and MHPG. We used the ratio of urine DA/HVA, a rough index of DA turnover. The cannula was flushed with NaCl 0.9% to ensure the cannula remained open. Plasma was separated and frozen before blind batch analysis. PRL was measured by time-resolved fluoroimmunoassay (DELFIA Prolactin, Wallac Oy, Turku, Finland). The samples were not run in one assay-run to mimic the real diagnostic procedure. The total assay variation ranged from 5.8-7.6%. HVA, VMA and MHPG levels were measured with reverse phase high performance liquid chromatography (RP-HPLC) and coulometric electrochemical detection (ECD), with a modified method essentially according to Hartleb et al [20]. Intra and inter-assay variation, calculated on low, mid and high levels, ranged from 1.2 to 7.8 % (intra-assay) and 4.8 - 10.4 % (inter-assay) respectively. Concentrations of HVA, VMA, MHPG, DA and NE in urine were determined using RP-HPLC with ECD and fluorometric detection [1,37]. For HVA, VMA and MHPG variation calculated on 3 different levels ranged from 1.2 to 4.1 % (intra-assay) and 3.6 - 8.5 % (inter-assay) respectively. For DA and NE variation ranges from 2.4 to 4.1 % (intra-assay) and 2.7 – 6.7 % (inter-assay) were calculated.

DNA Extraction and Genetic Analysis

Blood samples were collected from all subjects for DNA isolation. Genomic deoxyribonucleic acid (DNA) was extracted using a filter-based method (QIAamp DNA Mini Kit, Qiagen Ltd, UK). The COMT Val158Met polymorphism (rs4680) was genotyped using single-base primer extension and analyzed by matrix-assisted laser-desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) on a Bruker Ili Daltonics Mass Spectrometer as described previously [33]. All DNA samples were genotyped in duplicate to ensure reliability.

Statistical Analysis

Compiled data are expressed as mean ± SD. Between-group comparisons were performed by using independent-sample t-tests and factorial ANOVA or repeated-measure ANOVA with group (22q11DS or controls) × effect interaction, as appropriate for the dopaminergic markers. A probability value of 0.05 two-tailed was selected as significance level. Statistical analyses were performed with SPSS, release 12.0.1 for Windows (SPSS Inc., Chicago, IL, USA, 2003). The ΔPRL values were calculated by subtracting baseline values from the maximum levels post-AMPT administration.
RESULTS
Demographic Data
Twelve 22q11DS subjects and 12 age- and sex- matched controls, aged 18-39 years completed the protocol. The age (mean ± SD) of the subjects was 27.3 ± 7.0 and 26.5 ± 6.2 years, respectively. There were seven females and five males in both groups. One 22q11DS subject smoked. Full-scale intelligence was 79.8 (SD = 9.3) in the 22q11DS subjects.

COMT Genotype
Ten 22q11DS subjects had the Met allele and two had the Val allele. One control subject had the Met/Met genotype, four the Val/Val genotype and seven the Val/Met genotype.

Dopamine Depletion
All but three subjects reported feeling tired after oral AMPT intake. This effect resolved spontaneously within the first hours after the last AMPT administration. Three 22q11DS subjects mentioned feeling better, pleasant or calm up to 24 h following AMPT intake. No serious adverse events like acute dystonia or crystalluria were present. AMPT levels were obtained in all subjects after a 3 (T3) and 6 hour (T6) period following the first AMPT administration. No between-group differences were found. At T3, AMPT plasma levels were 12.58 mg/L ± 7.21 (mean ± SD; n = 12) in 22q11DS subjects and 17.68 ± 7.87 (n = 12) in controls. At T6, AMPT plasma levels were 15.80 ± 3.64 (n = 12) in 22q11DS subjects and 17.56 ± 5.32 (n = 11) in controls.

Neuro-Endocrine Response
The PRL level of one female 22q11DS subject was far outside normal limits at baseline (82.0 μg/L). As this is a pathological finding, also in 22q11DS, this subject was removed from further analysis. Baseline values of PRL were not significantly different between 22q11DS subjects (9.3 ± 3.5μg/L, n = 11) and controls (12.7 ± 7.8, n = 12; figure 1). PRL values increased in all subjects within the three hour period following the first AMPT administration and dropped subsequently at T6 in all except one subject with 22q11DS. The PRL response of subjects with 22q11DS were significantly lower at T3 (P = 0.04) than those of the controls (56.7 ± 23.5, n = 11 vs 86.8 ± 39.6, n = 12). There were no significant between-group differences at T6 (37.8 ± 16.2, n = 11 and 47.5 ± 20.4, n = 12 respectively). There was a trend towards significance between the groups for ΔPRL (48.8 ± 22.4, n = 11 in 22q11DS subjects vs 75.0 ± 40.6, n = 12, P = 0.072). A one-way repeated measure ANOVA showed a significant effect of group (P = 0.02), sex (P < 0.0005), time (P < 0.0005), and time by sex interaction (P = 0.001). Female subjects showed higher PRL responses than men. There was no significant group by time interaction.
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Figure 1.
Mean plasma prolactin (PRL, μg/L) levels following alpha-methyl-para-tyrosine (AMPT) administration in subjects with 22q11DS and controls. Error bars indicate SEM (+, P < 0.05; independent-sample t-test comparing measurements of 22q11DS and controls).

Peripheral Dopaminergic Markers

At baseline, urine DA levels were significantly (P = 0.04) higher in the 22q11DS subjects than in controls (203.7 ± 66.4 nmol/mmol kreat, n = 11 vs 154.7 ± 33.4, n = 12; figure 2a). We found no significant between-group differences for DA at T6 (97.2 ± 27.4, n = 11 vs 88.3 ± 37.9, n = 12). There was a trend for lower urine HVA levels at baseline in the 22q11DS group (1.8 ± 0.46 μmol/mmol kreat, n = 12 vs 2.5 ± 1.0, n = 12, P = 0.051; figure 2b). Urine HVA levels were significantly (P = 0.04) lower in the 22q11DS subjects at T6 (1.1 ± 0.3, n = 11 vs 1.8 ± 1.0, n = 12). DA/HVA ratios were significantly higher (P = 0.004) in the 22q11DS subjects than in controls (110.3 ± 36.5 vs 68.4 ± 23.8) at baseline as well as at T6 (P = 0.037, 54.0 ± 17.1 vs 37.5 ± 18.4; figure 2c).

HVA levels in plasma were significantly lower at baseline (T0), T3, and T6 (baseline: 46.73 ± 18.40 nmol/L, n = 12 vs 76.13 ± 24.83, n = 12, P < 0.01; T3: 32.14 ± 10.19, n = 12, vs 50.68 ± 22.16, n = 12, P = 0.02 and T6: 21.06 ± 6.71, n = 11, vs 33.40 ± 15.34, n = 12, P = 0.02; figure 2d) in the 22q11DS group as compared to the control group. Plasma HVA levels dropped in all subjects at T3 and at T6 in all except one adult with 22q11DS. Repeated measures ANOVA for urine DA showed a significant effect of group (P = 0.03) and time (P < 0.0005) and group by time interaction (P = 0.01). Repeated measures for urine and plasma HVA showed a significant effect of group (urine: P = 0.03, plasma: P < 0.001) and time (urine and plasma: P < 0.0005), but no significant group by time interaction.
Peripheral dopaminergic markers in subjects with 22q11DS and controls. Error bars indicate SEM (*, \(P < 0.01\); +, \(P < 0.05\); independent-sample t-test comparing measurements of 22q11DS and controls). (a) Mean urine dopamine (DA, nmol/mmol kreat) response to AMPT. (b) Mean urine homovanillic acid (HVA, \(\mu\)mmol/mmol kreat) response to AMPT. (c) DA/HVA ratio response to AMPT. (d) Mean plasma HVA (nmol/L) response to AMPT.

Peripheral Markers for Norepinephrine

We found no significant between-group differences for NE (figure 3a) at baseline and \(T_0\). There were no between-group differences for the NE metabolites vanilmandelic acid (VMA; figure 3b) and 3-methoxy-4-hydroxy-phenylglycol (MHPG; figure 3c) at \(T_0\) in urine. There was a trend for lower urine MHPG levels in the 22q11DS subjects at \(T_0\) (1.1 ± 0.2 \(\mu\)mmol/mmol kreat, \(n = 9\) vs 1.4 ± 0.3, \(n = 10\), \(P = 0.053\)). There were no between-group differences for VMA at \(T_0\). We found no between-group differences for NE/MHPG or NE/VMA ratios at baseline and after AMPT administration.

In plasma there were no significant between group differences for plasma levels of VMA and MHPG at baseline or at \(T_3\) and \(T_6\) (figure 3d,e). Plasma VMA and MHPG levels dropped in all but four (three adults with 22q11DS) respectively three subjects (one 22q11DS subject) at \(T_3\) and subsequently dropped in all respectively four (one adult with 22q11DS) subjects at \(T_6\). Repeated measures ANOVA did not show a significant effect of group or group by time interaction for any of the NE markers, except for MHPG in urine (effect of group, \(P = 0.04\)). Except for MHPG in urine all markers showed significant effect of time (NE urine: \(P = 0.001\), MHPG plasma: \(P = 0.01\), VMA urine: \(P < 0.0005\), VMA plasma: \(P < 0.0005\)).
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Figure 3.
Peripheral markers for nor-epinephrine (NE) in subjects with 22q11DS and controls. Error bars indicate SEM (a) Mean urine NE (nmol/mmol kreat) response to AMPT. (b) Mean urine 3-methoxy-4-hydroxy-phenylglycol (MHPG, μmol/mmol kreat) response to AMPT. (c) Mean plasma MHPG (nmol/L) response to AMPT. (d) Mean urine vanillylmandelic acid (VMA, μmol/mmol kreat) response to AMPT. (e) Mean plasma VMA (nmol/L) response to AMPT.

22q11DS: Met Only
Owing to the unequal distribution of the COMT genotype, we re-analyzed the Met-only 22q11DS subgroup controlling for gender, as the gender distribution was not equal anymore. After exclusion of the two 22q11DS subjects who were Val-hemizygous between-group differences for urinary DA and plasma HVA at T₀, T₃, T₆ remained significant.
DISCUSSION

In this first controlled study investigating dopaminergic neurotransmission in people with 22q11DS, we demonstrate disrupted dopaminergic neurotransmission. Our main findings are: (1) higher urine DA levels and lower plasma levels of the predominant metabolite (HVA) in 22q11DS subjects compared to controls at baseline; (2) lower plasma and urine HVA levels in 22q11DS subjects following DA depletion; (3) a higher DA/HVA ratio in the 22q11DS subjects at baseline and after DA depletion; (4) a lower PRL response following DA depletion in 22q11DS subjects.

It has been hypothesized that in 22q11DS subjects COMT haploinsufficiency may cause decreased COMT enzyme activity and hence an increase in brain DA levels [9,17,18]. Our findings in the peripheral dopaminergic markers are in line with such a ‘hyperdopaminergic state’. High DA levels could explain the increased risk for neuropsychiatric disorders in 22q11DS including psychosis, irritability and agitation as has been suggested by the inverted U-shaped curve model [15]. This paradigm emphasizes that DA should vary between optimal levels and that both increased and decreased DA levels may be associated with cognitive and/or psychiatric problems. Further support for excessive DA levels in 22q11DS subjects comes from the fact that three of our study subjects reported subjective improvements following AMPT administration with similar findings reported by Graf et al [18].

In keeping with our hypothesis, at baseline significantly higher urine DA levels and lower plasma HVA levels were observed in 22q11DS compared to controls (figure 2). There was a trend for lower urine HVA levels in 22q11DS subjects. Moreover, lower plasma and urine HVA levels were seen following administration of AMPT. Urine DA levels decreased faster in the 22q11DS group following AMPT administration. The reason for this is unclear. Furthermore, the ratio of DA/HVA, was higher in the 22q11DS subjects, both at baseline and after DA depletion, suggesting lower breakdown of DA as a result of COMT haploinsufficiency. As expected, no significant between-group differences in NE or its metabolites were demonstrated at baseline and after AMPT administration (figure 3). However, there is a differential COMT gene expression [38], a variation in COMT affinity and capacity for catecholamines [39] and variation in COMT activity [7,22,26] in various human tissues. There is also an important diversity and complexity of DA transmission in cortical and subcortical regions of the brain. Therefore, it is unclear what the consequence of COMT haploinsufficiency is on catecholamine levels and metabolites in different brain areas.

In contrast to our hypothesis we did not find any between-group difference in baseline PRL levels. Hypothalamic DA is the predominant inhibiting factor of PRL secretion in humans [13]. Therefore, if 22q11DS subjects have decreased capacity to degrade DA, lower PRL values in 22q11DS subjects would be the expected result. DA however, is not the only factor controlling PRL levels and the complex interaction of PRL-inhibiting and releasing factors is not completely understood [13]. For example, the DA level in hypophysial stalk plasma is five to seven times lower in male than in female, while plasma PRL levels are not much different [13]. In addition, COMT activity in brain becomes
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probably more important under challenged conditions: in COMT deficient mice, normal hypothalamic DA levels were found under normal conditions, but hypothalamic DA levels were disturbed after DA challenge [22]. Thus our findings are in agreement with those findings in COMT-deficient mice: following DA depletion, people with 22q11DS had significant lower PRL responses. A higher inhibitory hypothalamic dopaminergic tone in people with 22q11DS resulting from minimalized and comparable DA production in both groups, but less DA catabolism in the 22q11DS subjects could be an explanation for this finding. Therefore, it might well be that the dopaminergic neurotransmission system can compensate for COMT haploinsufficiency under normal conditions, but that such compensation fails under challenge. If this notion is correct, this would reject the concept of a simple hyperdopaminergic state. Moreover, some findings which appear to be elicited by stress that frequently occur in the syndrome, such as temper outbursts [5] and aggressive behaviour [23], could be better understood by this assumption.

As observed previously by others [27,32,41,42], AMPT administration increased PRL levels significantly shortly after its first administration and subsequently fell, in spite of comparable AMPT levels at T3 and T6. We assume that PRL levels at T3 were lower due to other factors, like somatostatin and γ-aminobutyric acid (GABA) or regulation from lactotrophs themselves [13]. The apparent discrepancy between a short neuro-endocrine peak response and a linear fall in peripheral dopaminergic markers is consistent with other studies applying the AMPT paradigm in humans [13,32].

Our study has several strengths. It has been suggested that COMT activity matures during adolescence [40]. Since we only included adults, it is likely that COMT activity had reached maturity in our subjects, and therefore interindividual differences in COMT activity due different stages in maturation unlikely confounded our results. In addition, influence of sex or age differences is unlikely, since all controls were age- and gender matched. Moreover, none of the participants had a history of psychiatric disorders, or had used antipsychotic- or psychostimulant medication.

Our study has also potential limitations. First, there are possible influences of the phase of menstrual cycle in women, for which we did not correct. For example, female PRL levels fluctuate during the menstrual cycle [19]. As expected, women had larger PRL responses than men, however even after controlling for gender the group differences remained. Second, as only two 22q11DS subjects were Val-hemizygous, no conclusions can be drawn from this subgroup. Future research should address this issue. Third, the sample size is relatively small and may have resulted in a limited statistical power. However, as noted by others, effect sizes for abnormalities in 22q11DS subjects are relatively large [8].
In conclusion, this study for the first time, demonstrates disrupted dopaminergic neurotransmission, in healthy, high-functioning adults with 22q11DS, using peripheral and neuro-endocrine dopaminergic markers. This disruption, possibly due to COMT haploinsufficiency, may partially contribute to the increased risk for neuropsychiatric disorders in this syndrome. Functional neuroimaging studies will increase our knowledge on the etiology of psychopathology in 22q11DS.

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DISCLOSURE/CONFLICTS OF INTEREST
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