Dopaminergic neurotransmission and cognitive decline in velocardiofacial syndrome

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1. How functions the dopaminergic neurotransmission in adult patients with VCFS who are functioning on an intellectual level of moderate to severe impairment (IQ < 55) by a) a strong cognitive decline or b) a premorbid level of functioning.2. Is...

Ethical review	Not approved
Status	Will not start
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON31666

Source
ToetsingOnline

Brief title
Dementia in VCFS

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
cognitive decline, dementia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: NARSAD

Intervention

Keyword: Dementia, Dopaminergic neurotransmission, Velocardiofacial syndrome

Outcome measures

Primary outcome

In plasma (T0,3,6) : HVA, MHPG, VMA, prolactine, level AMPT, proline

In urine (T0,6): HVA, MHPG, VMA, dopamine and norepinephrine, proline

Genotype (DNA isolation T0): COMT Val/Met polymorphism, other COMT polymorphisms.

COMT enzyme activity in erytrocytes or lymphocytes

Secondary outcome

Extrapyridamal side effects; IQ; Dementia rating scales (DMR and DSDS); psychiatric symptomatology (PASSAD); behaviour checklists (ABCL and SGZ); IQ measurements with Wechsler IQ scales

Study description

Background summary

Most patients with VCFS function intellectual on a borderline or mild disabled level. Many (± 30%) develop psychotic disorders and schizophrenia. For that reason it can give insight in pathophysiology of psychosis. Within the 22q11. region there are several candidate genes of schizophrenia. The gene coding for catechol-O-methyl-transferase (COMT) lies in this region and is one of the most serious candidate gene for schizophrenia and other psychiatric disorders. It is responsible for katabolism of the catecholamines. A deletion of 22q11.2 results most of the time in a haplo-insufficiency of the COMT gene which can result in increase of dopamine brain concentration and a risk in developing a psychosis. In our population, non-psychotic VCFS patients, we recently found a disturbed dopaminergic neurotransmission. A subcategory VCFS patients, suffering from severe psychosis, develop a severe cognitive decline. Also some patients function on a lower intellectual level (without a decline) as described in literature. Is unclear until now if these phenomenon*s can be attributed to

disfunctioning of the catecholaminergic neurotransmitter system compared to patients with VCFS that function better. Also we wonder if AMPT intervention could be of any benefit in mentioned subpopulation as described before.

Study objective

1. How functions the dopaminergic neurotransmission in adult patients with VCFS who are functioning on an intellectual level of moderate to severe impairment (IQ < 55) by a) a strong cognitive decline or b) a premorbid level of functioning.
2. Is it possible after the one time gift (challenge) to forsee the effects of the trial?
3. How will these patients react on a trial of four weeks AMPT (1 g daily) intervention.
4. Is there a connection between a low active COMT gene, the length of the deletion or other genotypes or haplo-insufficiencies?
5. Describe the behavioural phenotype of patients with VFS and an IQ below 55.

Study design

Administering AMPT in a fixed once only dose of 1,5 gram and a short trial of 4 weeks twice daily 0,5 gram AMPT

Intervention

Once only administration (orally) of 1,5 gram AMPT (challenge). In advance en afterwards determination of parameters in blood and urine.
4 week AMPT trial of twice daily administration of 0,5 gram AMPT

Study burden and risks

Participants can feel sedated and slight dejected. Eventually one may experience extrapyramidal side effects. Also restlessness is described. Eventually benzodiazepines can be administered to give some relieve.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Possession of del 22q11.2
Premorbid IQ of above 70 en now below 55
Premorbid IQ below 55
Only for the intervention group: serious behavioural and/or refractory psychiatric problems to treatment so far

Exclusion criteria

pregnancy

Study design

Design

Study type:	Interventional
Intervention model:	Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	01-07-2008
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Demser
Generic name:	Metyrosine, alpha-methyl-L-tyrosine or AMPT

Ethics review

Not approved

Date:	22-07-2008
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2006-003979-12-NL
CCMO	NL21082.000.08