APC & Behaviour

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal tract disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON41579

Source
ToetsingOnline

Brief title
n.v.t.

Condition

- Gastrointestinal tract disorders congenital
- Cognitive and attention disorders and disturbances

Synonym
Attention disorder

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Autism Spectrum Disorders, Children, Familial Adenomatous Polyposis Coli (FAP)

Outcome measures

Primary outcome

The main outcome parameter is the SRS score which can be considered a continuous response variable. The primary statistical approach will consist of standard ANOVA statistics for the comparison of SRS score means between cases and controls, while including confounding factors (for instance gender and clinical burden) into the analysis.

Secondary outcome

not applicable

Study description

Background summary

Autism Spectrum Disorders
All Autism Spectrum Disorders (ASDs) are developmental disorders, symptoms of ASD are expressed pervasively and appear early in the development of affected individuals. The defects that characterize ASD occur in the domains of communication and social interaction. Together with rigidity, insistence on sameness and a tendency towards obsessive, repetitive behaviors, these symptoms often remain manifest throughout the entire life of affected individuals. The autistic spectrum ranges from severe cases (the core syndrome called autism or autistic disorder) to milder forms which include pervasive developmental disorder, not otherwise specified (PDD-NOS) and Asperger syndrome.

ASDs have a major impact on human well-being and represent a large economic burden to our society. The long term prognosis of autism is unfavorable. Although there is variability, there is an average tendency for developmental regression during childhood. Even when restricting the follow-up to autistic individuals with relatively better cognitive abilities (performance IQ>50), only about 12% acquire a high level of independence in adulthood, 10 % require a minimal degree of support in daily living but is able to hold a job, 19% require support and supervision but have some degree of independence outside a specialized residence, 46% need a high level of support within a specialized residential setting and 12% are in need of high level hospital care 16.

To date no treatment for ASDs is available

Despite the huge progress medical science has made over the past few decades, is it to date still not possible to cure ASD. Pharmacotherapy is sometimes used to reduce undesired behaviors such as irritability or aggressive behaviors. However, to date no effective medication is available against the core deficits of ASDs, such as the social and communicative impairments. The main reason for the current lack of a safe and effective treatment for ASD is that the biological processes underlying this group of disorders are not well understood. Thus, improving the understanding of the biology of ASDs is a crucial step required for future development of better and effective treatment methods.

With the aforementioned identification of rare variants with large effect, a novel strategy has become possible. Instead of starting with the phenotype (ASD) in order to study the possible role of a genotype (a genetic variant) it is now feasible to bring together a group of individuals who share the same genetic variant and subsequently compare phenotypic characteristics of this group compared to individuals without that particular genotype. In other words; a reversed approach starting with the genotype in order to study the phenotype.

The fundamental and innovative characteristic of this approach is that any distinguishing phenotypic characteristic, if reliably and statistically confirmed, can be directly attributed to the effect of the genetic variant. Indeed, Abrahams and Geschwind recently argued that the study of subsets of ASD patients with specific genetic variants is likely to yield valuable information with regard to specific behavioral effects of particular variants1.

Stratification of the ASD population is likely to increase efficacy of treatment

Based upon the rationale explained above we propose that:

1. Studying the behavioral phenotype of ASD samples collected on the basis of shared genetic variants has the potential to dissect the clinical phenotype of ASD into a number of behavioral components and their underlying genetic etiology.
2. Studying the neurobiology of ASD samples collected on the basis of shared genetic variants can identify specific neurobiological pathways relevant to the (behavioral components of) the ASD phenotype.

For example; it is well known that mutations in the MECP2 gene lead to a specific subtype of ASD, Rett Syndrome3, 25. Girls with the MECP2 mutation display characteristic ASD symptoms including stereotypic movements of the hands. Therefore one can conclude that, amongst others, the MECP2 gene is relevant with regard to the development of stereotypic motor behavior7. Studies on the function of MECP2 and the neurobiological pathway in which it is involved in the brain will therefore likely shed light on the underlying neurobiology of stereotypic motor behavior. If, in the best of scenarios, this

leads to the development of novel treatment options, this knowledge can be used to target the intervention to the subpopulation of ASD patients with predominant stereotyped motor movements.
Similarly we recently studied ASD patients with Klinefelter Syndrome or the 22q11.2 Deletion Syndrome, and reported that ASD patient groups with a specific underlying genetic etiology demonstrate an autistic symptom profile that can be delineated from the general ASD population and has less heterogenic properties9. The fact that specific genetic etiologies translate into distinguishable ASD sub-phenotypes strongly suggest that these genetic subpopulations may also benefit from distinctive treatment approaches.

A need for the identification of genetic variants with behavioral effects
The field of autism research, and indeed, of the entire field of behavioral science would greatly benefit from the identification of genetic variants associated with specific behavioral phenotypes. This reversed phenotyping approach will likely yield a better understanding of the biologic underpinning of ASD and its phenotypic behavioral components. In addition, this could be the first step towards the development of medication or other interventions that may be specific for subgroups of ASD patients. For instance, the behavioral and cognitive impairments found in fragile X patients are caused by a genetic variant (not a CNV) in the gene FMR1. Subsequent studies have shown that the biological pathway affected by this gene dysfunction includes the metabotropic glutamate receptor 5 pathway, resulting in excess signaling. Studies with antagonist agents of this pathway have shown valuable effects on behavior and cognition, as well as on seizures, in animals15. Currently, the first trials with this agent have been initiated in individuals with fragile X syndrome.
The reversed phenotyping approach is hindered by the fact that most variants with modest to large effect size on (components of) the ASD phenotype occur at a low rate in the population. This makes it difficult to obtain sufficiently large samples. For instance, findings of several studies strongly suggest that certain genetic variations in the Neuroligins genes (NLGNs) contribute to the causation of ASDs13, 18. However, the rarity of each of these variations in ASD patients obstructs any attempt to study a sizeable sample of subjects with the same NLGN gene variant.

Mutations in the APC gene, a pivotal player in the Wnt pathway, lead to FAP
Familial adenomatous polyposis coli (FAP) is a heritable autosomal dominant intestinal disease characterized by the development of large bowel adenomatous polyps in the large intestine. Without treatment a progression to colorectal cancer will occur in nearly all cases12. The genetic etiology of FAP is autosomal dominant and consists of a mutation in a gene located on 5q21 which has been named the Adenomatous Polyposis Coli (APC) gene12. The APC gene plays a pivotal role in the Wnt pathway, a regulatory pathway that is important for numerous developmental processes. APC forms a multiprotein complex which

downregulates β-catenin, an activator of the transcription of several target genes in the Wnt cascade. When APC is impaired in its function, β-catenin can accumulate and generate abnormal expression of various genes affecting key developmental processes, including apoptosis, migration and differentiation14.

The Wnt pathway is thought to be a central actor in cell development
Interestingly, the Wnt pathway also plays a role in the development of the central nervous system28 as as well as in the maintenance and function of the adult brain17.
Several genes within this pathway have been associated with ASD susceptibility; notably Wnt2 and EN2 11, although the association in these genes was not consistently replicated, as is the case in most candidate gene studies in neuropsychiatric disorders. Interestingly, the genes TSC1 and TSC2, of which variations can cause tuberous sclerosis, alter the function of β-catenin and the subsequent Wnt cascade22. In 20 - 25% of patients with tuberosclerosis autistic behavioural features can be identified29. Importantly, the APC gene is highly expressed in the fetal and adult human brain (see APC gene expression figure: adapted from: http://smd.stanford.edu/cgi-bin/source/sourceSearch). Recently it was shown that APC is a key coordinator for presynaptic and postsynaptic maturation by providing anchorage to Neurexin and Neuroligin, providing further evidence for an important role of APC in brain development23.

Study objective

The above anounced studies suggest that some abnormalities in the Wnt pathway can be expected to affect development and function of the brain, potentially leading to recognizable behavioural phenotypes. Given the key role of APC in the Wnt pathway, and more specifically, in synaptic maturation, it is not unlikely that impaired function of the APC gene can be associated with neurodevelopmental disorders. Indeed, among the first papers indicating the role of the APC gene in FAP was a case report in which an autistic FAP patient with a deletion of the APC gene was described 6. In addition, a recent retrospective case-control study (autistic individuals versus controls) reported a significant association of the APC gene variation in cases30. Given these associations, the aim of the current study is to investigate whether the APC mutation, associated with FAP, also leads to a behavioural phenotype

Hypothesis: Carriers of FAP-associated APC mutations display a higher rate of behavioural abnormalities in the autistic spectrum compared to controls with the APC wild type alleles.

Study design

Statistical methods, Sample size, power calculation
Normative and clinical threshold scores recently assessed in a German

population8 will be used as set points for this study. The average SRS score in a typically developing childhood sample was found to be 25 with standard deviations of 15. The threshold for clinical relevance is 59. Above this threshold the presence of social behavioural pathology (autism spectrum disorders in particular) becomes more likely.
By including 100 cases and two groups of 100 controls we will have a power of 0.81 to detect a difference between case and control groups means of 6 points. Differences in mean scores of 10 points or larger have greater clinical relevance and can be detected with a power of 0.99. Type I error probability rate is set at 0.05, two tailed.

A two-step behavioral assessment protocol
The first stage of behavioural assessment will be performed using a questionnaire sent by letter mail and to be filled out by parents or caregivers, as well as the proband. After completion, the questionnaires are to be returned using a prestamped return envelop.

For the behavioural assessment of the first stage will be used:
1. Social Responsiveness Scale (SRS10), a written 65 item questionnaire. A self report will be filled out by the participant and a reference report will be filled out by the parents or caregivers of the participants. The SRS is well-validated against the gold standard clinical assessment for autism diagnosis, the ADI-R and the ADOS20, 21.
2. Child Behavior Checklist (CBCL), a written 103 item questionnaire. Again a self report (Youth Self Report, YSR) as well as a parental report (CBCL) will be used2
3. Global enquiry of social economic and educational level of the child and their parents. Age of each parent at birth of the child will be asked. Assessment of clinical burden to be filled out by parents and children.

The second stage of the assessment protocol concerns only those probands that show SRS scores in the clinical range, suggestive of the presence of an autism spectrum disorder. At this stage it is difficult to predict what exact proportion of the participants will have clinical range SRS scores and thus will be invited to participate in the second assessment. At any rate, this proportion is unlikely to be more than 20%, as higher prevalence of autism spectrum disorders amongst FAP children would certainly have been picked up and reported in the literature.

The behavioural assessment of the second stage will consist of a standard clinical evaluation, according to the guidelines of good clinical practice. This assessment will be performed by a Child and Adolescent Psychiatrist in those cases with SRS scores within the clinical range. If applicable, a DSM-IV based diagnosis will be made and adequate medical care will be provided. Zie Flow chart bijlage ...

Study burden and risks

not applicable

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Familial adenomatous polyposis coli (FAP) with confirmed APC mutation
Age in range 8-25 years

Exclusion criteria

Unwillingness or unability to give informed consent

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-01-2012
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	15-11-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
CCMO	NL36177.018.11