Case report

Altered functioning of the cingulate gyrus in two cases of chromosome 22q11 deletion syndrome

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Abstract

The 22q11 microdeletion syndrome (22q11-DS) is strongly associated with schizophreniform disorders and, in turn, the 22q11 deletion region harbours several candidate genes for schizophrenia. Here, we present the case of an adolescent female patient with 22q11-DS associated with impaired cognitive abilities and behavioural abnormalities. The patient was studied with magnetic resonance imaging (MRI) and positron emission tomography (PET) as well as extensive neurophysiological investigations. Although no structural or functional abnormalities were found in MRI and PET, assessment of event-related potentials elicited during the Continuous Performance Test revealed a lack of NoGo anteriorisation. The latter was replicated in a second case of 22q11-DS with schizoaffective disorder but devoid of a severe somatic syndrome. This electrophysiological finding, which indicates modified functioning of the cingulate gyrus, has previously been demonstrated only in patients suffering from schizophrenia and attention deficit/hyperactivity disorder, two psychopathological conditions frequently associated with 22q11-DS. We conclude that more extensive study of NoGo anteriorisation as a potential endophenotype of 22q11-DS patients at risk for 22q11-associated psychiatric conditions is warranted.

Keywords: Schizophrenia; Attention deficit hyperactivity disorder; Brain mapping; Continuous Performance Test; Electrophysiology; Positron emission tomography

1. Introduction

The 22q11 deletion syndrome (22q11-DS; MIM #192430) is characterised by a microdeletion of chromosome 22q11, which usually comprises three Megabases. The deletion is transmitted dominantly. The majority of patients, however, suffer from a de novo mutation. The phenotype of 22q11-DS, which occurs in approximately 1 of 4000 live births and thus is relatively frequent, is broad and includes such symptoms as congenital heart abnormalities, immune deficiency with thymal aplasia, velocar-yngeal insufficiency and slight dysmophy with characteristic facies, but also severe syndromal developmental abnormalities with mental retarda-
tion. However, all attempts to link symptomatology to distinct genes have thus far been unsuccessful. Most probably, gene × gene, gene × environment interactions or epigenetic phenomena play an important role.

It is now well established that 22q11-DS is associated with an increased rate of psychiatric disorders including schizophreniform and affective psychoses, as well as attention deficit/hyperactivity disorder (ADHD). Epidemiological data from several independent studies indicate that 22q11-DS is an important genetic risk factor for schizophrenia (Sz) or bipolar psychosis, and several linkage analyses likewise demonstrated 22q11 to be a susceptibility region for Sz and bipolar disorder (for review, see Murphy and Owen, 2001; Murphy, 2002). Those findings prompted several groups to look for Sz candidate genes at the 22q11 locus. As a result, several genes have been shown to be associated with Sz by SNP or haplotype analysis. Most interestingly, the gene for catechol-O-methyltransferase (COMT) for which a gene/dose-dependent increase in the genetic risk to develop Sz has been shown is located at the 22q11 locus. Other candidate genes with substantial evidence include PRODH, PRODH2, DGCR6, NOGO-R and KIAA1292. PIK4CA, UFD1L and SNAP29 have also been suggested, although less convincingly. Taken together, the findings suggest that there is no major gene effect in the deleted region but that several genes with minor influence cause psychiatric symptoms in 22q11-DS.

In patients suffering from Sz or ADHD, an altered function of the prefrontal cortex and in particular of the anterior cingulate cortex has been demonstrated during various cognitive activation tasks. NoGo anteriorisation (NGA), as a two-dimensional topographical measure of event-related potentials elicited during the execution (Go) and the inhibition (NoGo) conditions of the Continuous Performance Test (CPT), allows an assessment of anterior cingulate function (Fallgatter et al., 2002) with extraordinarily high interindividual stability and short- as well as long-term test–retest reliability. Based on these findings, our hypothesis was that 22q11-DS patients would be characterised by diminished or absent NGA as an electrophysiological indicator of altered prefrontal brain function.

2. Methods

2.1. Continuous Performance Test

Letters were presented to both patients sequentially and in pseudorandom order in the centre of a computer screen between two vertical fixation lines. The presentation time was 200 ms, and the interstimulus interval was 1650 ms. The instruction was to press the response button as fast as possible every time the letter “O” was followed directly by the letter “X”. The letter “O” thus was a primer to prepare a motor response (80 primer conditions), whereas “X” served as a target when directly following an “O” (40 Go conditions). The other letters were either signals to inhibit the prepared motor response when directly following “O” (40 NoGo conditions) or were otherwise meaningless distractors (240 distractor conditions). The patient performed a short training session to ensure correct understanding of the instructions.

A 21-channel EEG was recorded during performance of the Go-NoGo task (CPT). All correct and artifact-free responses were averaged to one event-related potential in the Go (30 trials) and the NoGo (28 trials) conditions. For topographical analysis, the locations of the centroids were computed at the individual Global Field Power peaks (Lehmann and Skrandies, 1980) in a P300 time window (277–434 ms poststimulus). At the individual GFP peaks, the locations of the centroids (amplitude-weighted locations of the positive and the negative components of the brain electrical landscape) were computed. The locations of the Go and NoGo centroids were quantified in the anterior–posterior axis by a coordinate system resulting from the planar projection of the electrode array onto a rectangular grid (Lehmann, 1987). The subtraction of the value of the NoGo centroid from the Go centroid of the same subject resulted in the individual quantified NoGo-anteriorisation, which is a topographical measure independent of individual potential latency (Fallgatter et al., 1997).

3. Case reports

Case 1: An 18-year-old female was admitted to our department for diagnostic evaluation and socio-
therapy. Her somatic history was remarkable: she suffered from a complex congenital heart anomaly, requiring cardiac surgery three times. Furthermore, decreased T-cell numbers had been diagnosed in her infancy, although without immunopathy. She suffered from velopharyngeal insufficiency resulting in nasal speech and snoring. Genetic investigation revealed a microdeletion at 22q11. A de novo mutation was assumed, as no other family members had similar symptoms or severe diseases at all, including neuropsychiatric disorders (both parents were independently interviewed by an experienced psychiatrist); however, genetic testing was refused by both parents.

The patient showed developmental delay, and milestones were reached later than would normally be expected. Thereafter, specific cognitive deficits were noted resulting in learning disabilities, especially in mathematical and spatial–logical tasks. Verbal and mnestic abilities, however, seemed normal. The patient completed regular school with problems. Psychiatric symptoms consisted of reduced frustration tolerance, social withdrawal, lack of motivation, depressive episodes and suicidality. Due to these problems, she had psychotherapy and a brief prior psychiatric admission leading to the diagnosis of a major depressive episode.

Extensive psychiatric evaluation was performed by three experienced psychiatrists (A.R., A.J.F. and K.-P.L.) in free and semi-structured interviews. She appeared to be a friendly and open adolescent. Cognitive abilities did not seem to be grossly impaired, but the ability to abstract was reduced. There were no delusional thoughts or hallucinations. Her affect was slightly blunted and flattened; she appeared to be careless about her future, and inadequately happy, yet not completely fulfilling the diagnostic criteria of hebephrenic schizophrenia but reminiscent of a prodromal state of this disorder. Otherwise, no axis I disorders according to the ICD-10 classification system could be positively diagnosed. Physical examination revealed a systolic heart murmur, high palate and small ears, but no gross dysmorphic signs or other pathologies. We attributed all psychiatric symptoms to 22q11-DS and initiated behavioural psychotherapy; psychotropic medication was not introduced.

Case 2: To confirm the validity of the electrophysiological alterations (see below), we examined a second case (22-year-old female) with cytogenetically confirmed de novo 22q11-DS. Apart from a slightly dysmorphic face and high palate due to submucosal cleft palate, there were no somatic symptoms, especially no heart anomaly and no immune deficiency, explaining why the diagnosis was made as late as in her 18th year. During high school, the patient became detracted and depressed, beginning at age 16. She became socially withdrawn, developed erotomania as well as persecutory delusions and depressed mood. The symptoms fluctuated, yet did not resolve completely, leading to four stays in psychiatric hospitals. On admission to our department, she displayed negative symptoms in that she lacked motivation and drive; she was socially withdrawn. Delusions were present, but not marked, and mood was slightly depressed. She appeared distrustful and suspicious, but not irritable or aggressive. Vague acoustic hallucinations in the form of commenting voices were infrequently disturbing her. Thus, as signs of both affective and schizophrenic psychosis were present, we applied a diagnosis of schizodepressive disorder according to ICD-10.

3.1. Laboratory and additional findings

Routine laboratory examinations were normal in both cases; thyroglobuline antibodies were markedly elevated (>3000 IU/ml) in case 1, suggesting autoimmune thyropathy, which has been suggested to be associated with 22q11-DS (Kawame et al., 2001). Scintigraphic and sonographic examination of the thyroid gland however did not show abnormalities. Speckled ANA antibodies were elevated in case 1 at 1:320 in the absence of corresponding symptoms. T-cell counts were in the normal range as were serum calcium. The definitive diagnosis of 22q11-DS was made by FISH analysis utilising an AppligeneOncor probe (methods and data available on request) in both cases.

3.2. Psychometric profile

Patient 1 reached 8 points in the DemTect test, corresponding to mild cognitive impairment. Average IQ was 78, as evidenced by the HAWIE-R test, with
no prominent differences between verbal and executive abilities. The Benton test indicated the presence of cerebral dysfunctioning (4 correct results, 6 errors; expected: 7/5). The Wisconsin Card Sorting Test was conducted to examine prefrontal executive functions. In five out of six trials, the patient correctly identified the hidden rule. Total errors were slightly below average (standard value, 82), but perseverative errors were in the normal range (standard value, 91). Case 2 displayed under-average IQ in the range between 60 and 70, as evidenced by the CFT20 test.

3.3. Neuroimaging

Cranial MRI showed a small cerebellum typical for 22q11-DS in case 1, but no further abnormalities; cranial MRI in case 2 was normal. Positron emission tomography with fluorodeoxyglucose-F18 (case 1 only) was entirely normal (data and methods available on request).

3.4. Electrophysiological investigations

On a behavioural level, case 1’s test performance was absolutely normal in this easy version of the CPT, with two errors of omission and one error of commission, compared with 77 correct responses. Case 2 reached comparable values (five errors of omission, zero errors of commission). The topographical ERP analysis of case 1 displayed an abnormal result, with the centroid in the NoGo condition (3.88) being more posteriorly located than in the Go condition (3.22) on an anterior–posterior axis (Fig. 1). Therefore, the resulting value for the NGA was negative (−0.66), indicating a lack of the physiological NoGo anteriorisation phenomenon. Similar values were obtained when case 2 was examined: the Go-centroid was 3.56 (latency of GFP 395 ms; GFP, amplitude 7.37 μV), and the NoGo centroid was 3.54 (GFP latency: 410 ms with a GFP amplitude of 5.03 μV), resulting in a NGA of 0.02, i.e.
an apparently absent NGA far below the normal range (0.6 to 1.1).

4. Discussion

As evidenced by FISH examination, our patients suffered from 22q11-DS with complex heart abnormality and velopharyngeal insufficiency as lead symptoms in case 1. Psychopathologically, case 1 displayed a typical neuropsychological profile and low-average IQ. Further psychiatric signs were flattened and blunted affect, social withdrawal, decreased motivation and frustration tolerance, and a history of depressive episodes, which all are typical for adolescent 22q11-DS patients (Murphy and Owen, 2001). The patient did not suffer from psychosis, but in view of her young age, we consider her to be at high risk to develop schizophreniform or bipolar psychosis due to these prodromal symptoms. Interestingly, glucose brain metabolism, as evidenced by positron emission tomography, seemed to be normal, as was cranial MRI apart from decreased cerebellar size. The latter is known to occur in about one third of all 22q11-DS patients (Chow et al., 1999; Van Amelsvoort et al., 2001). Case 2 displayed symptoms of schizoaffective disorder, as well as submucosal cleft palate, but she had no other pathology and cranial magnetic resonance imaging was also normal. These results do not argue for any gross structural or functional brain deficits in 22q11-DS.

Notably, both patients displayed abnormal NoGo anteriorisation elicited during the CPT. This parameter quantifies the shift or anteriorisation of the positive brain electrical field that is usually observed during NoGo conditions, when a prepared motor response has to be inhibited. The NGA has been interpreted as a neurophysiological correlate of response inhibition or prefrontal response control and has been suggested to reflect functioning of the anterior cingulate cortex. In addition to the anterior cingulate cortex, other nearby brain areas such as the dorsolateral prefrontal cortex or the supplementary motor area could contribute to abnormal NoGo anteriorisation, although LORETA analysis in previous studies argues against this interpretation (Fallgarter et al., 2002). So far, NoGo anteriorisation has been observed in every single healthy subject investigated in three subsequent studies (Fallgatter et al., 1997, 2000; Fallgatter and Strik, 1999), and has only been found to be deficient in schizophrenic patients (Fallgatter and Müller, 2001) as well as in adult patients with probable ADHD during childhood, also in the absence of psychotropic medication. Both groups of patients are therefore assumed to exhibit deficits in prefrontal response control. This also seems to be true for the patients reported here, since they showed no anteriorisation of the brain electrical field during the CPT NoGo condition, as indicated by a negative or zero NGA value. Because schizophrenic disorders and ADHD are psychiatric conditions associated with 22q11-DS, indicating that this genetic abnormality comprises alterations in prefrontal brain function as detectable via the measurement of NoGo anteriorisation, this finding may be of particular interest.

In conclusion, we suggest that the lack of NoGo anteriorisation represents a possible endophenotype for 22q11-DS related psychiatric conditions. This finding requires replication in a larger set of 22q11-DS patients, and it may be meaningful to follow up these patients to determine whether pathological NoGo anteriorisation is a predictor for the development of psychosis or associated with 22q11-DS in general. Finally, all known 22q11-DS patients are recommended for psychiatric assessment due to the increased risk of psychiatric disorders. NoGo anteriorisation in this context might serve as an easy test to determine a non-invasive surrogate parameter in identifying patients at high risk for developing psychiatric symptoms.

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References


