

Chromosomal abnormalities in clinical psychiatry: a report of two older patients

W.M.A. Verhoeven^{*,}**
J.H.A.M. Tuerlings^{*}
C.M.A. van Ravenswaay-Arts^{*}**
J.A.J. Boermans^{*}
S. Tuinier^{*}

^{*} Vincent van Gogh Institute for Psychiatry,
Venray

^{**} Erasmus University Medical Centre,
Department of Psychiatry, Rotterdam

^{***} Radboud University Medical Centre,
Department of Human Genetics, Nijmegen

THE NETHERLANDS

ABSTRACT – Background and Objectives: In clinical psychiatry genetic anomalies are infrequently part of the differential diagnosis, especially in the elderly. Two case reports are used to illustrate the relevance of a genetic workup for diagnosis, treatment and prognosis.

Methods: A female and a male patient, aged 81 and 68 year respectively, were admitted because of psychotic symptoms. Despite their relatively low level of intelligence together with autistic-like behaviour in the female patient and dysmorphias in the male patient, a genetic disorder was previously never considered.

Results: In the female patient a balanced translocation between chromosomes X and 19 was found, while in the male patient a mosaic trisomy 8 was demonstrated.

Conclusions: Genetic analysis is indicated in patients with autism, lower intelligence, unexplained somatic anomalies and dysmorphias.

Received 27 September 2006

Revised 17 January 2007

Accepted 23 January 2007

Introduction

In older psychiatric patients genetic anomalies are usually not considered as relevant

part of the differential diagnosis since it is the general feeling that such disorders have already been diagnosed at an earlier age. In this group of patients, however, ‘earlier age’ means 40 years ago or more, which refers to

a period in which genetics was still in its infancy. Because of the rapid developments in genetics, the de-institutionalization of people with mental retardation and their increasing life expectancy, clinical psychiatry is confronted with extra differential diagnostic options: genetic syndromes that may be associated with specific psychopathology, the so called behavioural phenotypes^{1,2} The diagnostic process, however, is seriously hampered by on the one hand a lack of knowledge about psychopathology in rare genetic diseases and the natural course of these disorders³ and on the other hand the assumption that one specific genetic disorder is implicated in psychiatric syndromes⁴.

To our knowledge, the possibility of a genetic syndrome that may be part of the differential diagnosis is rarely thought of in psychiatric patients of advanced age. Since the diagnosis of a genetic syndrome may have therapeutic consequences, including a genetic workup is worthwhile. This was previously illustrated by the case of a 70-year-old female patient in whom after a hospitalization of more than 40 years, a diagnosis of 22q11 deletion syndrome was made⁵. Recently, two older patients were hospitalized because of psychotic symptoms. In both patients a cytogenetic abnormality was found that was previously not considered.

Case reports

Patient A is a 81-year-old single female who was hospitalized for the first time because of disorientation, self neglect, wandering, paranoid ideation and psychomotor agitation. Her history showed a long lasting social incompetence, paranoid attitude and social isolation. No formal psychiatric diagnosis was made There were no physical

abnormalities and she had in the past a normal menstrual cycle.

At psychiatric examination, the patient was neglected and disoriented in trias. She was not able to concentrate and she suffered from insomnia. There were no hallucinations. Her thinking was incoherent and had a paranoid structure. She had a dysphoric mood and her intelligence was estimated to be lower than average. Information from the heteroanamnesis demonstrated that the patient had always been a withdrawn person with impairment of social interactions and autistic behaviours like: stereotypies, diminished eye to eye gaze and a reduced emotional reciprocity. Physical and neurological examination did not reveal major abnormalities. There were no dysmorphic features. An ECG showed atrium fibrillation and an incomplete right block. MRI-scanning of the brain showed apart from a slight atrophy, normal for the age, no abnormalities. An initial diagnose of delirium due to an urinary tract infection was made for which she was treated with an antibiotic and a low dose of haloperidol. After recovery, the patient developed a major depressive disorder with psychotic features (nihilistic delusions). Subsequently, she was treated with citalopram. Because of non-response to citalopram, treatment with nortriptyline in a daily dose of 25 mg (plasma concentration 22µgr/l) was started that resulted in a remission within 6 weeks. Her autistic behaviours persisted.

Because of her subaverage intellectual functioning and pre-existent autistic-like behaviours, extensive neuropsychological examination as well as a genetic analysis was performed. Neuropsychological evaluation demonstrated a total IQ of 82 (WAIS-III; performat: 78, verbal: 88) and a reduced psychomotor activity. In addition, concentration was slightly impaired. No further cognitive impairments could be established.

Genetic analysis (Figure 1) showed a balanced translocation between the short arm of chromosome X and the long arm of chromosome 19 [46,X,t(X;19)(p11.4;q13.3)]. Subsequently, a comparative genomic hybridization (CGH) array (whole genome; ~32,000 clones with average resolution of 300 kb; UCSC genome browser, release May 2004) did not show additional abnormalities.

Patient B is a 68-year-old male with a mild mental retardation. He was firstly admitted at the age of 36 because of a so called 'Profschizophrenie', characterized by paranoid ideation, manifold disinhibition, dysphoric mood, chaotic behaviour and confusion. Three years later, he developed a relapse, this time a psychotic disorder with catatonia. A third psychotic episode with

manifest mood symptoms occurred at the age 42. Thereafter the patient remained free of psychotic symptoms for a period of 10 years during which he was treated with fluphenazine decanoate.

At the age of 52, he was hospitalized for the fourth time because of a psychotic deterioration with prominent affective and catatonic features. A diagnosis of schizoaffective disorder was made. Psychological testing showed a total IQ of 65 (WAIS, per-formal: 60, verbal: 74). Since then he lived in a sheltered care facility and was admitted several times in the psychiatric hospital for relapsing psychotic episodes and treated with various antipsychotics, antidepressants and Lithium. At the age of 68, the patient was hospitalized again.

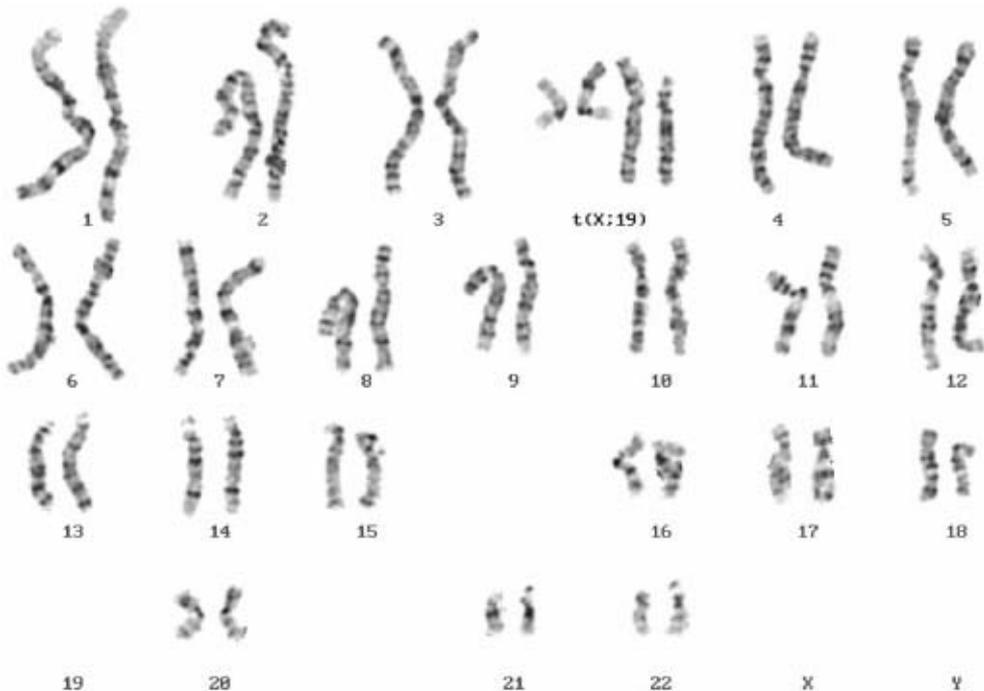


Figure 1. Karyotype of patient A. The chromosomes 19 and X are depicted between the chromosomes 3 and 4. The left chromosome is the normal chromosome 19 upside down. Also the translocation 19 (2nd chromosome) is upside down with part of chromosome Xp translocated on 19q. The third chromosome is the normal X and the right chromosome the translocation X, with the short arm replaced by a small part of 19q.

At admission he presented with catatonic symptoms like mutism, mannerisms and stereotypies. Thereafter, a fluctuating psychopathological picture emerged, in that catatonic symptoms alternated with psychomotor agitation, perplexity, anxieties, visual hallucinations and paranoid ideation. A diagnosis of acute polymorphic psychotic disorder was made (ICD-10: F23.0). Somatic examination revealed a short stature (153 cm) with disproportional short arms, legs, hands and feet, a small head circumference (53 cm) and an abnormal sternum. No facial dysmorphias were present. X-rays of the skeleton demonstrated multiple cartilaginous exostoses of the arms and legs. CT-

scanning of the brain revealed no abnormalities. An ECG was normal. Chromosomal analysis showed a normal karyotype in cultured lymphocytes. Since his clinical features were suggestive for a possible (micro) deletion of the long arm of chromosome 8 or a mosaic trisomy 8, CGH array was performed that showed an increased density for all markers located on chromosome 8, indicative for a mosaic trisomy 8 which was confirmed by FISH technique (Figure 2).

The patient was successfully treated with haloperidol and valproic acid and discharged to a nursing home. Within a short period of time he died from an acute cardiac failure.

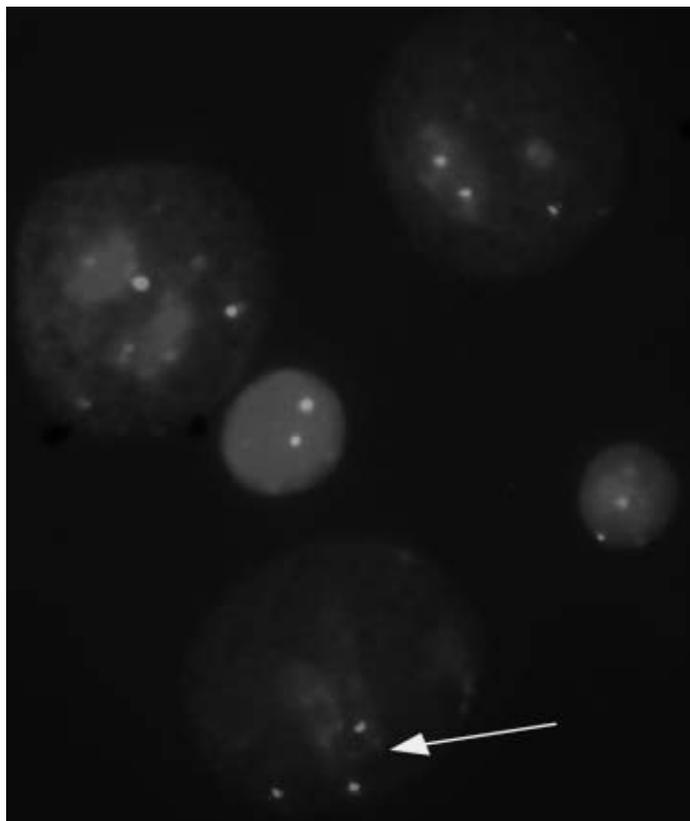


Figure 2. FISH confirmation of mosaic trisomy 8 in patient B. In a minority of interphase nuclei three signals (arrow) can be seen with a centromere probe of chromosome 8.

Discussion

In both patients genetic examination demonstrated abnormalities that were not known previously, albeit that patient B was known for his mild mental retardation and relapsing atypical psychoses and patient A for her autistic-like behaviour.

In patient B, trisomy 8 mosaicism was found that is not extremely rare and was first described in the seventies of the past century by De Crouchy et al.⁶. This syndrome is characterized by facial dysmorphias, various skeletal abnormalities and mental retardation, like in the present case, and may be associated with genitourinary, cardiovascular and ophthalmologic abnormalities⁷⁻¹⁰. Psychiatric comorbidity, including a so called behavioural phenotype, has not been reported as yet in this chromosomal disorder. The mosaic trisomy could not be demonstrated with routine chromosome studies due to the low percentage of abnormal cells. It is well known that in mosaic trisomy the mosaicism in peripheral blood cells decreases with age.

In patient A, a previously not described chromosomal abnormality associated with autistic characteristics was demonstrated. This finding illustrates the importance of looking for medical and genetic disorders as a cause of autistic behaviour as strongly advocated by Gillberg and co-workers¹¹⁻¹³.

These case reports illustrate that clinical genetics is of growing importance in geriatric psychiatry too and that the results may be relevant for both the neuropsychiatric differential diagnosis as well as treatment and for recognition of somatic comorbidity. In psychiatric patients who show autism, lower intelligence, dysmorphias or specific somatic abnormalities, a genetic analysis may be worthwhile.

References

1. Turk J, Hill P. Behavioral phenotypes in dysmorphic syndromes. *Clinical Dysmorphology* 1995; 4(2): 105-115.
2. Verhoeven WMA, Siiben AES, Tuiner S. Psychiatric consultation in intellectual disability; Dimensions, domains and vulnerability. *Eur J Psychiat* 2004; 18(1): 31-43.
3. Verhoeven WMA, Hendrikx JLM, Doorackers MC, Egger JIM, Van Der Burgt I, Tuinier S. Alexithymia in Noonan syndrome. *Genet Counsel* 2004; 15(1): 47-52.
4. Kendler KS. Reflections on the relationship between psychiatric genetics and psychiatric nosology. *Am J Psychiat* 2006; 163(7): 1138-1146.
5. Verhoeven WMA, Tuinier S, Engelen JJM, Hollanders-Crombach HTM, Curfs LMG. Velo-Cardio-Facial syndrome: Clinical report of a 70-year-old woman. *Am J Med Genet* 2002; 111(4): 409-411.
6. De Crouchy J, Turleau C, Léonard C. Etude en fluorescence d'une trisomie c mosaïque, probablement 8: 46,XY/ 47,XY, ?8+. *Ann Genet* 1971; 14: 69-72.
7. Berry AC, Mutton DE, Lewis DGM. Mosaicism and trisomy-8 syndrome. *Clin Genet* 1978; 14(2): 105-114.
8. Nakajima Y, Watarida S, Onoe M, Sugita T, Nojima T, Mori A. Surgical repair of a ventricular septal-defect in a patient with trisomy-8 syndrome. *J Cardiovasc Surg* 1995; 36(2): 171-173.
9. Dougall TW, Gibson PH. Bilateral, asymmetrical congenital dislocation of the radial heads in trisomy 8 syndrome. *Bull Hosp Jt Dis* 1997; 56(2): 113-4.
10. Stone DU, Siatkowski RM. Congenital retinal dystrophy and corneal opacity in trisomy 8 mosaicism. *J Aapos* 2005; 9(3): 290-291.
11. Gillberg C, Coleman M. Autism and medical disorders: A review of the literature. *Dev Med Child Neurol* 1996; 38(3): 191-202.
12. Gillberg C. Chromosomal disorders and autism. *J Autism Dev Disord* 1998; 28(5): 415-425.
13. Miller MT, Stromland K, Ventura L, Johansson M, Bandim JM, Gillberg C. Autism associated with conditions characterized by developmental errors in early embryogenesis: a mini review. *Int J Dev Neurosci* 2005; 23(2-3): 201-219.

Address for correspondence:

Prof. Dr. Willem M.A. Verhoeven, M.D., Ph.D.
 Vincent van Gogh Institute for Psychiatry
 Stationsweg 46, 5803 AC Venray
 The Netherlands
 Phone: +31478527339
 Fax: +31478527110
 e-mail: wverhoeven@vvgi.nl