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The study on the occurrence of the 22q11.2 deletion in patients affected with a psychiatric disease

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SUMMARY

Aim. The aim of the study was estimation of the rate of deletion 22q11.2 among psychiatric patients and an attempt at assessment of the degree in which this rate is influenced by coexistence of dismorphic features and congenital defects.

Material and methods. Cytogenetic examination was performed in 255 patients with psychosis. Patients were divided into two groups: group I composed of 61 patients with psychosis and at least two phenotypic features characteristic of 22q11.2 deletion syndrome (22q11DS), and group II composed of 194 patients with psychosis without phenotypic features of 22q11DS. Banding and fluorescence in situ hybridization (FISH) techniques were applied.

Results. 22q11.2 deletion was found in 3/61 patients of group I (4.9%) and in 3/255 all the psychiatric patients studied (1.2%). This incidence was significantly higher than in the general population ($p<0.001$). The frequency of the deletion among psychiatric patients revealing phenotypic features of 22q11DS: 3/61 (4.9%) ($p<0.0001$) was even higher. In all cases with the deletion, the phenotype was characteristic of 22q11DS.

Conclusions. Firstly, 22q11.2 deletion was found to be 40 times more common among psychiatric patients than than the general population; sex chromosome aberrations were also significantly more common than in the general population. Secondly, the presence of dysmorphic features and some congenital defects in psychiatric patients increases the rate of 22q11.2 deletion significantly.

schizophrenia / 22q11.2 deletion syndrome / phenotypic features

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INTRODUCTION

Epidemiological studies show a considerable contribution of genetic factors in the aetiology of schizophrenia [1, 2], however family and twin studies [3] did not allow to identify the responsible gene or genes. Chromosome regions showing linkage with schizophrenia are as follows: 1q21-q22, 5q21-q31, 6p24-q22, 6q16-q25, 8p21-p22, 10p15-p11, 13q14.1-q32, 15q14, 22q-1-q22 [4].

Chromosomal aberrations are more common among the subjects with schizophrenia than in the general population, sex chromosomal aber-

rations are also significantly higher. In the past several years much attention was focused in the analysis of 22q11.2 region deletion observed in the 22q11.2 deletion syndromes (22q11DS). 22q11.2 deletion is connected with characteristic clinical features (phenotype). Facial abnormalities, otholaryngological abnormalities, cardiac defects (especially of the conotruncal origin), different degree of thymic and parathyroid glands hypoplasia, even aplasia are observed. Speech abnormalities and learning difficulties are also reported. Mental development is usually borderline low; mild and moderate intellectual disability is rarely observed [6, 7]. In neuroimaging, a small cerebellum, hiperintensities in the white matter, agenesis of corpus callosum, and developmental malformations of septum pellucidum are observed. A total decrease of the size of the brain was stated as well as disturbances in the brain development which are described as a disproportion between white and grey matter in different structures of the brain.

Several genes were localized in the 22q11.2 region. Particular attention was paid to the gene localized in this region coding catechol-O-methyl transferase (COMT) – the enzyme involved in dopamine degradation pathway. However association between different alleles of this enzyme and schizophrenia was not found [9, 10].

The aim of this study was to estimate the frequency of the 22q11.2 deletion among psychiatric patients and to assess the degree in which this frequency depends on the coexistence of dysmorphic features or congenital defects.

MATERIAL AND METHODS

Psychiatric Departments all over Poland were invited to take part in our study but most of the cases were collected among patients admitted to the Institute of Psychiatry and Neurology. For the purpose of proper selection of the patients a standardised questionnaire, taking into account the diagnosis of a psychiatric disorder and the phenotypic features of 22q11.2 syndrome was used.

Cytogenetic examination was performed in 255 patients with schizophrenia, bipolar disorder, schizoaffective disorder and obsessive compulsive disorders diagnosed according to ICD-10. Because of the small number of cases the last three psychoses were analysed together as "other psychoses". All patients were divided into two groups. Group I was composed of 61 patients with psychosis and at least two phenotypic features characteristic for 22q11.2 DS, while group II was composed of 194 patients with a psychosis but without phenotypic features of 22q11.2 or with only one phenotypic feature of 22q11.2 DS. Cytogenetic examinations were performed in samples of peripheral blood lymphocytes. Chromosomes were stained using routine banding methods (GTG banding technique was used in all cases, in some cases BCG and NOR technique were applied). Lymphocytes were cultured for 72 hours at 37ºC in complete medium (LymphoGrow) according to the method of Moorhed at al. [11]. GTG banding pattern was obtained using tripsin and Giemsa stain (Seabright [12]). To detect or to exclude 22q11.2 deletion fluorescence in situ hybridization (FISH) analysis was used in all the cases. Two probes specific for 22q11.2 deletion were used: Tuple 1 and N25 (Cytocell). To control correctness of hybridization reaction, a control probe of the subtelomeric region of the q arm of chromosome 22 was used. Hybrydization was performed according to the manufacturer's (Cytocell) procedure. Additional examinations: CT, EEG, EKG and laryngologic examination were performed in patients in whom 22q11.2 deletion was detected .

RESULTS

In group I schizophrenia was diagnosed in 34 patients and other psychoses were diagnosed in 27 individuals. Group II was composed of 194 patients: schizophrenia was diagnosed in 161 patients and other psychoses were diagnosed in 33 of them. The most frequent abnormalities observed in group I were: dysmorphic face, otolaryngological anomalies, impairment of individual development such as mental and learning disabilities. Among patients with dysmorphia of the face, the most frequently observed features were: long narrow face – 32 cases, characteristic nose – 28 cases, small mouth – 21 cases. Among patients with otolaryngological anomalies in 24

nasalized speech was recorded. 15 patients had learning disabilities. Several other phenotypic features were diagnosed in some of the patients. Congenital heart disease was found only in two cases. Data about immunodeficiency or hypoplastic thymus during neonatology were very infrequently available neither were other abnormalities, such as those involving brain or kidney. Early onset of schizopherenia (first episode before the age of 15) was observed in 12 cases of group I and in 7 cases of group II (Tab. 1).

The results of cytogenetic examinations of the two groups of patients are presented in Table 1. 22q11.2 deletion was found in 3 of the 61 patients in group I (4.9%); schizophrenia was diagnosed in 2 of the patients with the deletion and depression in one of them. (Tab. 1, Fig.1, next page). Frequency of the 22q11.2 deletion among patients with schizophrenia and phenotypic features characteristics of 22q11.2 DS was 2 out of 34 (5.9%). Frequency of 22q11.2 deletion in the general population was estimated as 0.025% [13]. Therefore the observed frequency of 22q11.2 deletion in group I was significantly higher as compared to the general population ($p<0.0001$) (Tab. 1). Frequency of the deletion in all the studied groups was 3 of 255 (1.2%). This is also significantly higher then in the general population ($p<0.0001$) (Tab.1). Several phenotypic features characteristic of the 22q11.2 deletion were diagnosed in each patient with the deletion. More details concerning particular cases are presented below. Karyotypes of parents were normal in

Table 1. Results of cytogenetic examinations and the incidence of chromosomal aberrations in 225 patients with schizophrenia or other psychiatric disorders including division to the groups taking into account the age of onset of psychiatric disease++

Type of psychosis		Number of cases	Age of onset ≤15 years++	Type of chromosomal aberrations	Number of chromosomal aberrations (incidence)
Group	Schizophrenia	34	7	del 22q11.2 t (2;10) (q10;q10)	2 (5,9%)** 1 (2.9%)
	Other psychoses	27	5	del 22q11.2	1 (3,7%)**
	Total	61	12 (19.7%)	del 22q11.2 other chromosomal aberrations	3 (4,9%)** 1 (2.5%)
Group II	Schizophrenia	161	4	del 22q11.2 47,XYY 47,XXX[3]/46XX[17] 47,XXY[16]/46,XY[14]	0 1 1 1
	Other psychoses	33	3	del22q11.2	0
	Total	194	7 (3.6%)	del 22q11.2 other aberrations	0 3 (1.5%)*
Groups I& II Total		255	19 (7.5%)	del 22q11.2 other chromosomal aberrations	3 (1.2%)* 4 (1.6%)*
General population (Wilson et al.. 1994)					(0.025%)

+ in all cases examination was performed using the FISH technique with application of a probe specific to the 22q11.2 region
++ in patients of age in this range, neither del 22q11.2 syndrome nor any other chromosomal aberration were found

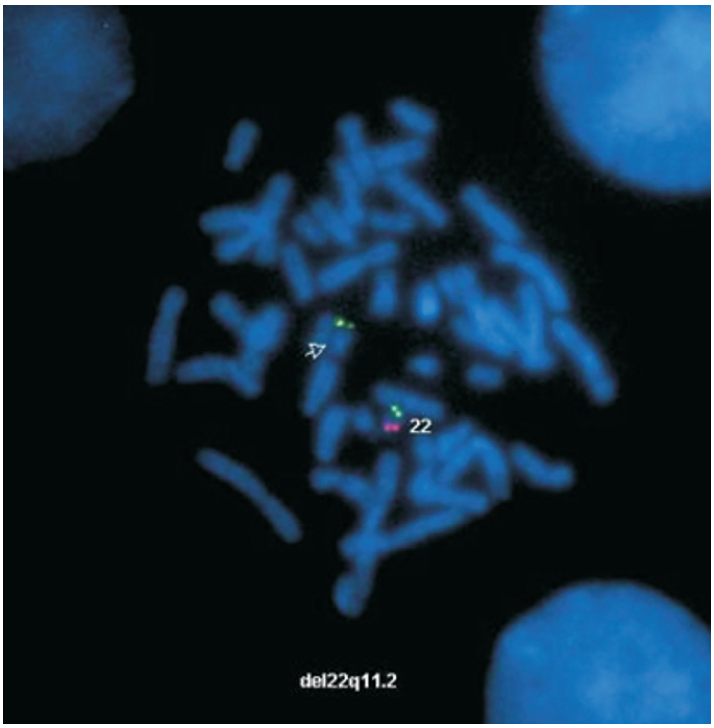

Fig. 1. 22q11.2 deletion. Examination performed in patent 1 using the FISH technique. Red signal – probe N25 specific to the 22q11.2 region. Green signal – control probe (in the q arm of chromosome 22). The arrow indicates the place of 22q11.2 deletion (lack of red signal)

all cases of 22q11.2 deletion; no psychiatric disorders in the patients families were observed.

In the other 58 patients of group I, one case of balanced reciprocal translocation t(2;10)(q10;q10) was found; It was not possible to determine whether the translocation was a familiar or a de novo one.

Cases of 22q11.2 deletion were not found among 194 patients of group II, (Tab.1), however three cases of sex chromosome abnormalities were detected: one case of 47,XYY, one case of 47,XXX and one case of 47,XXY (Klinefelter Syndrome). (Tab. 1) In the latter two cases of these chromosomal aberrations, mosaic karyotypes were found.

Case 1

A 16 year old boy, delivered at term after normal pregnancy and labour at 10 Apgar points. In the neonatal period, tremor of the limbs was observed. He also had a flatovalgus feet. His psychomotor development was delayed: started to walk at the age of 1 and half and talk at 3. He was diagnosed as a case of speech disorder. At the age of 14 the psychological evaluation proved the normal mental development with intelligence at the average level. EEG, ECG and Cardiac-echo were normal. Brain CT revealed cavum of septi pellucidi and mild enlargement of the fluid space over the frontal lobes. Abdominal CT proved the absence of a left kidney. Laryngological evaluation revealed significant deviation of the nasal septum. First symptoms of schizophrenia were noted at the age of 16 years.

Case 2

38 year old male. Delivered at term after normal pregnancy and labour at 9 Apgar points. At birth his weight was 2790g and length 54 cm. He was born with flatovalgus feet. Speech development was delayed. The learning difficulties were noted at secondary school. Laryngological evaluation revealed high-arched palate without a cleft. He also demonstrated nasal speech. Brain CT showed enlargement of the fluid space over the frontal and temporal lobes and over the cerebellum. Dilatation and dislocation of the ventricular system were not detected but cavum septum pellucidum was present.

Brain NMR revealed enlargement of the fluid space over the frontal and temporal lobes and over the cerebellum, insignificant dilatation of the ventricular system without dislocation and also cavum septum pellucidum-cavum Vergae

X-rays showed no abnormalities in the chest. Abdominal USG and mediastinum CT were also normal. ECG and Cardiac-echo were within the normal limits. First symptoms of schizophrenia appeared at the age of 17.

Case 3

26 years old male. Delivered at term after normal pregnancy and labour at 10 Apgar points. In the neonatal period feeding difficulties were observed. In childhood delayed psychomotor development and speech disorders were detected. The learning difficulties were noted in primary school.

Laryngological evaluation revealed a high-arched palate. EEG was normal. Brain CT showed non-specific focus in the left frontal lobe. At the age of 20 psychiatric symptoms of depression were first observed.

Teeth enamel dysplasia and malocclusion were observed. In Doppler sonography vascular changes were detected.

DISCUSSION

It is difficult to establish the frequency of 22q11.2 deletion in subjects with psychiatric disorders. Wilson et al. [13] reported that the frequency of this chromosomal aberration in general population is 1 for 4000 births (0.025%), while Botto et al. [14] found that it was less frequent – 1 in 5950 (0.017). It can be therefore estimated to be in the range 1 for 4000 to 1 in 6000. This aberration appears to be considerably frequent in subjects with schizophrenia. However, the estimated data obtained by various authors are different. Using the FISH technique in cytogenetic examinations Chow at al. [15] found 22q11.2 deletion in 2% of the cases; Karayiorgou et al. [16] in 4% and Arinami et al. [17] in 0.33%. Data of the present work are similar to those of Karayiogou et al. [16] because deletion was found in 2 of 195 (1%) subjects with schizophrenia. Frequency of the 22q11.2 deletion is then significantly higher as compared with general population (40 fold higher – $p<0.0010$). In group I, deletion was found in 3 of the 61 (4.9%) patients while in patients with schizophrenia with existing phenotypic features of 22q11.2 DS deletion was even more frequent – 2 of 34 (5.9%). Deletion was observed in 2 (1%) subjects of 195 our patients with schizophrenia. In the general population, frequency of schizophrenia is also estimated as 1%. Therefore it may be estimated that 22q11.2 deletion as the cause of schizophrenia occurs in general population with a frequency 1 in 10 000 (0.001).

Most of the data indicate that 22q11.2 deletion is associated with psychiatric diseases of an early onset, but in the study of Ivanow et al. [18] the deletion was not found in any of the 129 subjects with onset of psychiatric disease below the age of 18. Similarly, in this study deletion was not found in 19 subjects with early onset of psychiatric disease (age ≤ 15).

It is possible that these differences are caused by the different criteria of patient selection. Therefore the comparison of our data with data presented by other authors is difficult. It can be concluded that the present knowledge of 22q11.2 DS syndrome epidemiology is insufficient and that the study should be continued. Our observation that the deletion was more frequent among psychiatric patients who were revealing phenotypic features characteristic for 22q11.2 DS also show differences as compared with other authors results.; Gothelf and Lombroso [9] found the deletion in 20% of such cases and Basset et al. [19] found it even in 60% of them. Taking into account our results it seems that their data are to high probably because of a selection error. In this paper, similarly to Basset et al., a questionnaire concerning dysmorphic features was used , but it was created in a way which increased the probability of deletion detection. The most frequent of them is a characteristic face dysmorphy. In our practice the connection of dysmorphic face and otolaryngological anomalies with schizophrenia caused that our patients were sent to the hospital to look for 22q11.2 deletion and in this group, three cases of deletion were found. Higher frequency of 22q11.2 deletion observed in subjects with psychiatric diseases, particularly with schizophrenia give hope for the identification of a distinct subtype of schizophrenia. However up to now distinct differences in clinical descriptions between schizophrenia patients with deletion or without deletion were not found [20].

It should be added that among patients with psychosis other chromosomal aberrations were observed quite often, first of all sex chromosomal aberrations [5]. Kumra et al. [21] found Klinefelter syndrome in 10% of the patients with psychosis and Nicolson et al. [22] found Turner syndrome in 2% of the diagnosed subjects. In our material, the frequency of sex chromosomal aberrations was also significantly higher than it was in the general population; we found it in 3

of the 255 patients (1.2%) (Tab. 1) In the general population, sex chromosomal aberrations are at least 10 fold more rare.

CONCLUSIONS

1. 22q11.2 deletion is more frequent in subjects with psychiatric disease than in the general population. In our group of subjects sex chromosome aberrations were also more frequently found: 40 and 10 times more frequently respectively.

2. In the presence of phenotypic features of the 22q11.2 deletion syndrome in patients with psychiatric diseases, the frequency of the 22q11.2 deletion was high – it could be an indication to cytogenetic analysis using the FISH technique.

REFERENCES

1. Tsuang MT, Faraone S. The frustrating search for schizophrenia genes. Am J Med Genet. 2000; 97: 1–3.
2. Craddock N, O'Donovan MC, Owen MJ. The genetics of schizophrenia and bipolar disorder: dissecting psychosis. J Med Genet. 2005; 42; 193–204.
3. Gardno A, and Gottesman I I. Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and funtional genomics. Am J Med Genet. 2000; 97: 12–17.
4. Williams N, O'Donovan MC, Owen MJ. Genome scans and microarrays: converging on genes for schizophrenia? Genome Biol. 2002; 3: reviews 1011.1–1011.5
5. Bassett AS, Chow EW, Weksberg R. Chromosomal abnormalities and schizophrenia.Am J Med Genet. 2000: 97: 45–51.
6. Swillen A, Vandeputte L, Cracco J, Maes B, Ghesquiere P, Devriendt K, Fryns JP. Neuropsychological, learning and psychosocial profile of primary school aged children with the velo-cardio-facial syndrome (22q11 deletion): evidence for a nonverbal learning disability? Neuropsychol Dev Cogn Child Neuropsychol. 1999; 5: 230–41.
7. Swillen A, Devriendt K, Legius E, Prinzie P, Vogels A, Ghesquiere P, Fryns JP. The behavioural phenotype in velo-cardio–facial syndrome (VCFS): from infancy to adolescence. Genet Couns. 1999; 10: 79–88.
8. Chow E, Janiszewski E, Young D, Scutt L, Weksberg R, Bassett AS. Neuropsychological functionary in adults with 22q11 deletion syndrome and schizophrenia. Schizophr Res. 1999; 36: 88–89
9. Gothelf D and Lombroso PJ. Genetics of Childchood Disorders: XXV, Velocardiofacial Syndrome. J Am Child Adolesc Psychiatry 2001; 40: 489–491.
10. Rybakowski JK, Borkowska A, Czerski M, Hauser J. Eye movement disturbances in schizophrenia and polymorphism of catechol-O-methyltransferase gene. Psych Res. 2002; 113: 49–57.
11. Moorhead PS, Norwell PC, Melman WJ, Battisp DM and Hungerford DA. Chromosome preparation of leucocytes cultured from human peripheral blood. Exp. Cell Res. 1960; 20: 613–615.
12. Seabright M. Human chromosome banding. Lancet 1972; 1: 967.
13. Wilson DI, Cross IE, Wren C Scambler PJ, Burn J, Goodship J. Minimum prevalance of chromosome 22q11 deletions. Am J Hum Genet 1994; 55: A169.
14. Botto LD, May K, Fernhoff PM, Correa A, Coleman K, Rasmussen SA, Merritt RK, O'Leary LA, Wong LY, Elixson EM, Mahle WT and Campbell RM. A population-based study of the 22q11.2 deletion: phenotype, incidence, and contribution to major birth defects in the population. Pediatrics 2003; 112: 101–107.
15. Chow LY, Merce GB, Wing YK, Fung KP, Lee CY, Ungvari GS, and Waye M. Schizophrenia and deletion at 22q11 in Hong Kong Chinese. Am J Med Genet 1997; 74: 677.
16. Karayiorgou M, Galke B, Budarf M, Nestadt G, Antonarakis SE, Kazazian HH, Housman DE, Pulver AE. Further characterisation of the 22q11 schizophrenia susceptibility locus. Am J Med Genet. 1997; 74: 677.
17. Arinami T, Ohtsuki T, Takase K, Shimizu H, Yoshikawa T, Horigome H, Nakayama Y. Screening for 22q11 deletions in a schizophrenia population. Schi Res. 2001; 52: 167–170.
18. Ivanov D, Kirov G, Norton N, Williams HJ, Wiliams NM, Nikolov I, Tzwetkova R, Stambolova SM, Murphy KC, Toncheva D, Thrapar A, O'Donovan MC, and Owen MJ. Chromosome 22q11 deletions, velo-cardio-facial syndrome and early-onset psychosis. Br J Psych. 2003; 183: 409–413.
19. Bassett AS, Hodgkinson K, Chow EWC, Correia S, Scutt LE, Weksberg R. 22q11 Deletion Syndrome in adults with schizophrenia. Am J Med Genet (Neuropsychiatr Genet) 1998; 81: 328–337.
20. Bassett AS, Chow EWC, AbdelMalik F, Gheorghiu M, Husted J, Weksberg J. The schizophrenia phenotype in 22q11 deletion syndrome. Am J Psych. 2003; 160: 1580–1586.
21. Kumra S, Wiggs E, Krasnewich D, Meck J, Smith ACM, Bedwell J, Fernandez TLJ, Lenane M, Rapaport JL. Brief report: association of sex chromosome anomalies with childhood – onset psychotic disorders. J Am Acad Child Adolesc Psychiatry 1998; 37: 292–296.
22. Nicolson R, Giedd J N, Lenane M, Hamburger S, Singaracharlu S, Bedwell J, Fernandez T, Thaker GK, Malaspina D, Rapoport JL. Clinical and neurobiological correlates of cytogenetic abnormalities in childhood–onset schizophrenia. Am J Psychiatry 1999; 156: 1575–1579.
23. Connor JM, Ferguson-Smith MA Essential Medical Genetics, 4 Oxford, 1994, p. 127.