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Mental retardation as a risk factor to develop a psychotic disorder

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Introduction. One of the main aims of research on schizophrenia has been to pinpoint the early symptoms and signals of the disease before its appearance.

Objectives. We have examined the diagnoses previously given to patients before they were diagnosed of schizophrenia.

Method. This is a case-control study in which we used a data register including the fields of minimum basic data set (MBDS) whose time period included 1999 to 2005.

Results. In our study, there was a 3.6% frequency of mental retardation and 2.1% one of behavioral and emotional disorders with onset usually occurring in childhood and adolescence, both diagnosed previously. The estimated OR for a mentally retarded patient to suffer adult onset psychosis is 4.6 (95% CI [3.43-6.26]), schizophrenia 5.8 (95% CI [4.20-7.88]), paranoid schizophrenia 4.8 (95% CI [3.39 –6.93]), residual schizophrenia 7.0 (95% CI [4.81 -10.09]) and persistent delusional disorder 2.7 (95% CI [1.57 -4.73]).

Conclusions. It can be concluded from our study that there is an increased frequency of mental retardation among the pathological records of subjects who will be diagnosed with paranoid schizophrenia and residual schizophrenia in the future. This fact supports the etiological thesis of schizophrenia involving neurodevelopment disorders.

Key words:
Schizophrenia. Psychosis. Childhood. Mental retardation. Diagnosis.

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Retraso mental como factor de riesgo para el desarrollo de un trastorno psicótico

Introducción. En las últimas tres décadas uno de los principales objetivos de la investigación en esquizofrenia ha sido la identificación de los síntomas y signos precursores de la enfermedad antes de su aparición.

Objetivo. Buscamos en nuestro estudio los antecedentes que se otorgan previamente a pacientes antes de ser filiados como esquizofrenia.

Método. Se trata de un estudio caso-control sobre el que utilizamos un registro de datos que incluye los campos del Conjunto Mínimo Básico de Datos y el período de tiempo considerado fue entre 1999-2005.

Resultados. Encontramos una frecuencia de 3,6% de retraso mental y un 2,1% de antecedentes de trastornos del comportamiento y de las emociones de comienzo habitual en la infancia y adolescencia, ambos como diagnóstico previo. La *odds ratio* de que un paciente con retraso mental sufra psicosis en la edad adulta es de 4,6 (IC 95% [3,43-6,26]), esquizofrenia de 5,8 (IC 95% [4,20-7,88]), esquizofrenia paranoide de 4,8 (IC 95% [3,39 –6,93]), esquizofrenia residual de 7,0 (IC 95% [4,81 -10,09]), trastorno por ideas delirantes de 2,7 (IC 95% [1,57 -4,73]).

Conclusiones. De nuestro estudio se puede concluir que existe una frecuencia incrementada del diagnóstico de retraso mental entre los antecedentes patológicos de sujetos que posteriormente serán diagnosticados de esquizofrenia paranoide y esquizofrenia residual. Este hecho, supone un apoyo a la hipótesis etiológica de la esquizofrenia que involucra alteraciones en el neurodesarrollo.

Palabras clave:
Esquizofrenia. Psicosis. Infancia. Retraso mental. Diagnóstico.

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INTRODUCTION

In the last three decades, one of the main objectives of research in schizophrenia has been to identify the preceding symptoms and signs of the disease prior to its appearance, that is, the childhood background in adults who will develop schizophrenia. Many early signs of the disease have been described in the childhood period[1]. The strategies used to describe the signs and symptoms prior to psychosis have basically been selection of high risk groups, that is, selecting

children born to schizophrenic parents who have a 10% to 15% risk of adult schizophrenia[2-3]. Another study method on childhood background has been the longitudinal follow-up of families of adolescents with non-psychotic disorders. This is another group that can show increased risk of schizophrenia in the future[4]. Finally, another strategy is to study patients diagnosed of schizoid disorder and to investigate if they have sub-syndromic characteristics that could reflect vulnerability to psychosis[5].

Previous pictures found in young children and/our youth in the scientific literature associated to schizophrenia and/or psychosis are mental retardation and specific disorders of child development.

Regarding mental retardation as a previous background, there is an increase in the frequency of a background of this diagnosis in patients linked to the schizophreniform disorder spectrum[6-18]. In his study on the prevalence of psychiatric disease in patients with mental retardation, Lund[15] found 1.3% of patients with schizophrenia and 5% with unspecified psychosis, data similar to other studies[6-8, 11-14].

On the other hand, different studies[2,19-28] have established the relationship between disorders of early childhood development and psychotic disorders in the adult age. Standing out among these disorders are: anxiety, depression, attention deficit hyperactivity disorder (ADHD), childhood oppositional defiant disorder and conduct disorders[19], child autism and autistic spectrum disorder[20], child psychosis[21] and «child conduct disorders»[2,22-26].

Thus, we see that many studies, both retrospective and prospective[2,22-26], have found a relationship between childhood conduct disorders and schizophrenia in the adult age. Male patients who develop schizophrenia in the adult age have a higher prevalence than expected, one that is greater than in the general population, of having suffered behavior disorders in adolescence/early childhood[27].

The relationship between anxiety, depression, ADHD[19,29] and conduct disorder/oppositional defiant disorder in childhood in individuals who would be diagnosed of schizophreniform disorder later on has also been published[19]. Kim-Cohen et al.[19] observed that adults diagnosed of manic episode and schizophreniform disorder had a psychiatric background during adolescence. The authors concluded that half of the adult individuals who have criteria for a psychiatric diagnosis - according to the DSM-IV- at 26 years of age had a previously diagnosable disorder at ages ranging from 11 to 15 years and also that 3/4 of these individuals had a first diagnosis before 18 years of age.

Finally, the relationship between autistic spectrum disorders and the final diagnosis of schizophrenia and other psychoses has been established[27,30]. The study of Stahlberg et al.[20], who calculated the prevalence and comorbidity of psychotic and bipolar disorders in 241 adults with attention deficit hyperactivity disorder and/or autistic spectrum disorder, shows that there is a significant subgroup of adult patients with ADHD (10%) and/or autistic spectrum disorder (14.8%) who fulfill criteria for bipolar disorder with psychotic symptoms, schizophrenia and other psychotic disorders.

Based on the above studies, there seems to be a relationship between mental retardation and childhood development disorders with the possibility of developing a psychotic disorder in the adult age. Our study has focused on calculating the risk of developing psychosis in patients having a background of mental retardation and childhood development disorders.

METHODS

The information available on patients seen in a health care area made up by the a Fundación Jiménez Díaz as reference Hospital covering an area of approximately 300,000 inhabitants in Madrid and in Mental Health Centers of the Center of Madrid and the Arganzuela areas was analyzed. We used a data registry that included the field of the minimum basic set of data (MBSD) and the time period from 1999 to 2005. We analyzed the data related with the care given to patients who had any diagnosis of schizophrenia and/or psychotic disorder (ICD-10 F2). The study was approved by the Ethics Committee (EC) of the Fundación Jiménez Díaz and the Hospital Doce de Octubre of Madrid.

Our study is based on a clinical file that includes all the medical actions taken in the central areas of Madrid. This data base includes the out-patient visits made in two Mental Health Centers (MHC) and also includes the medical acts made in both the emergency service and in a brief hospitalization unit and in the out-patient clinics of the tertiary hospital covering this area.

The patients who had received medical care within the time period ranging from January 1, 2000 to December 21, 2004 (n = 22.859) were selected from the 37.205 patients in the registry.

The objective of our study was to discover the background that the patients selected had before finally being diagnosed of schizophrenia. Therefore, the frequency of the behavioral and emotional disorders with onset usually occurring in childhood and adolescence (ICD-10 F9) and background of mental retardation (ICD10 70-79) were compared in patients with and without schizophrenia and psychosis (ICD-10 F2). The methodological details of this study can be consulted in previously published articles[31, 32, 33].

RESULTS

Our results come from 22,859 patients, a total of 2,558 of whom had a final diagnosis of «psychosis and/or schizo-

phrenia» (11.19%). Table 1 shows the sociodemographic characteristics of the patients of the sample (n = 22,859; age at 1st visit, age at last visit, groups - age at 1st visit, groups - age at last visit, gender, civil status, education, living situation and work status).

Table 1 Sociodemographic characteristics of the sample (n=22,859)

Variables		Mean (SD)
Age 1st visit (years)		39.9 (19.1)
Age last visit (years)		42.5 (19.6)
		%
Age groups 1st visit (years)	0-14	7.6
	15-64	73.8
	65-74	6.2
	>75	5.2
	Losses	7.2
Age groups last visit (years)	0-14	6.3
	15-64	72.7
	65-74	6.7
	>75	7.0
	Losses	7.3
Gender	Man	1.0
	Woman	59.0

SD: standard deviation

Table 2 provides the summary of the diagnoses and frequencies of early childhood diagnoses and mental retardation (ICD-10 F70-99) of patients who had been diagnosed of schizophrenia and/or psychosis in the adult age. We have found a 3.6% frequency of mental retardation as previous diagnosis and 2.1% of background of behavioral and emotional disorders with onset usually occurring in childhood and adolescence.

In table 3, the frequencies of ICD 10 F70-79 (mental retardation) and ICD-10 F90-98 (behavioral and emotional disorders with onset usually occurring in childhood and adolescence) are compared in patients with and without diagnoses of psychoses, schizophrenia, residual and paranoid schizophrenia and persistent delusional ideas disorders.

The following data were obtained regarding previous diagnosis of mental retardation (F70-79). A total of 2.7% (n = 68) of the patients diagnosed of psychosis had a previous diagnosis of mental retardation versus 0.6% (n = 119) of those with no diagnosis of mental retardation (Fisher's exact statistics test $p < 0.001$). The estimated risk for a patient with mental retardation to suffer psychosis in the adult age is 4.6 (95% CI [3.43-6.26]). Among the patients diagnosed of schizophrenia, 3.4% (n = 58) of the patients had a previous diagnosis of mental retardation versus 0.6% (n = 129) among the remaining disorders (Fisher's test $p < 0.001$) and that the estimated risk that a patient with mental retardation would suffer schizophrenia in the adult age is 5.8 (95% CI [4.20-7.88]). Among the patients diagnosed of paranoid schizophrenia, 3.2% had a previous diagnosis of mental retardation and 0.7% other disorders (Fisher's exact statistics test $p < 0.001$). The estimated risk that a patient with mental retardation has to suffer paranoid schizophrenia in the adult age is 4.9 (95% CI [3.39-6.93]). Among the patients diagnosed of residual schizophrenia, 4.6% had a previous diagnosis of mental retardation and 0.7% other diagnoses (Fisher's exact statistics test $p < 0.005$) and the estimated risk that a patient with mental retardation would suffer residual schizophrenia is 7.0 (95% CI [4.81-10.10]).

Table 2 Frequencies of ICD 10 F70-99 diagnoses in patients with psychosis/schizophrenia

Diagnoses	%
F70-79 Mental retardation	**3.6**
F70 Mild mental retardation	2.4
F71 Moderate mental retardation	0.9
F72 Severe mental retardation	0.6
F73 Profound mental retardation	0.1
F79 Unspecified mental retardation	0.5
F80-89 Psychology development disorders	**0.6**
F81 Specific developmental disorders of scholastic skills	**0.1**
F81.0 Specific reading disorder	0.1
F83 Mixed specific developmental disorder	0.1
F84 Pervasive development disorders.	**0.4**
F84.3 Another disintegrative disorder of childhood	0.1
F84.5 Asperger's syndrome	0.3
F84.9 Pervasive developmental disorder, unspecified	0.1
F89 Unspecified disorder of psychological development	**0.1**
F90-98 Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	**2.1**
F91 Dissocial disorders	**0.5**
F91.1 Unsocialized conduct disorder in children	0.1
F91.2 Socialized conduct disorder in children	0.1
F91.9 Other unspecified conduct disorder	0.3
F92 Mixed disorder of conduct and emotions	**0.4**
F93 Emotional disorders with onset specific to childhood	**0.4**
F93.2 Social anxiety disorder of childhood	0.1
F93.3 Sibling rivalry disorder	0.2
F93.8 Other childhood emotional disorders	0.1
F95 Tic disorders	**0.1**
F98 Other behavioral and emotional disorders with onset usually occurring in childhood and adolescence	**0.7**
F98.0 Nonorganic enuresis	0.1
F98.1 Nonorganic encopresis	0.1
F98.8 Other specified behavioral and emotional disorders with onset usually occurring in childhood and adolescence	0.5
F99 Unspecified mental disorder	**0.1**

We obtained the following significant results regarding the previous diagnosis of behavioral and emotional disorders with onset usually occurring in childhood and adolescence (ICD-10

Table 3 **Frequencies of background of childhood diagnoses (Mental retardation, ICD -10 F70-79; and behavioral and emotional disorders with onset usually occurring in childhood and adolescence, F90-98) in adult patients with and without diagnoses of psychoses, schizophrenia, residual schizophrenia, paranoid schizophrenia and persistent delusional ideas disorder.**

Diagnoses	F70-79*					F90-98**				
	n	%	Odds Ratio	95% CI	Fischer´s Exact Test	n	%	Odds Ratio	95% CI	Fischer´s Exact Test
Psychoses **(F-20)**										
No (n=20.301)	119	0.6	4.6	3.43-6.26	p < 0.001	229	1.1	1.2	0.82-1.69	
Yes (n=2.558)	68	2.7				34	1.3			p = 0.378
Schizophrenia **(F20-F29)**										
No (n=21.158)	129	0.6	5.8	4.20-7.88		239	1.1	1.3	0.82-1.91	
Yes (n=1.701)	58	3.4			p < 0.001	24	1.4			p = 0.288
Schizophrenia Paranoid **(F20.0)**										
No (n=21.651)	148	0.7	4.9	3.39-6.93		243	1.1	1.5	0.94-2.35	
Yes (n=1.208)	39	3.2			p < 0.001	20	1.7			p = 0.095
Schizophrenia Residual **(F20.5)**										
No (n=22.073)	151	0.7	7.0	4.81-10.10		248	1.1	1.7	1.01–2.90	
Yes (n=786)	36	4.6			p < 0.005	15	1.9			p = 0.058
Persistent delusional disorder **(F22-F22.9)**										
No (n=22.192)	173	0.8	2.7	1.57-4.73		249	1.1	1.9	1.10–3.26	
Yes (n=667)	14	2.1			p < 0.005	14	2.1			p < 0.005

*F70-79: mental retardation; **F90-98: Behavioral and emotional disorders with onset usually occurring in childhood and adolescence.

F90-98). Among the patients diagnosed of persistent delusional ideas disorders, 2.1% had a previous diagnosis of behavioral and emotion disorder with onset usually occurring in childhood and adolescence and 1.1% had other disorders (Fisher's exact statistics test Fisher p < 0.005). The estimated risk that a patient with behavioral and emotion disorders with onset usually occurring in childhood and adolescence would suffer schizophrenia was 1.9 (95% CI [1.10–3.26]).

DISCUSSION

The results of our study show that 3.4% of adult schizophrenic patients had a psychiatric background of mental retardation and 1.4% had behavioral and emotional disorders with onset usually occurring in childhood and adolescence during their childhood. In the sample considered, the mental retardation diagnosis was associated with an increased risk (odds ratio) of 4.6 to present psychosis, of 5.8 for schizophrenia, of 7.0 for residual schizophrenia, of 5.0 for paranoid schizophrenia and of 2.7 for persistent delusional ideas disorder. Thus, an increased frequency of the diagnosis of mental retardation is found among the pathological background of subjects who are subsequently diagnosed of paranoid schizophrenia, residual schizophrenia and persistent delusional ideas disorder.

The impact of behavioral and emotional disorders with onset usually occurring in childhood and adolescence on the subsequent risk of developing psychosis and/or schizophrenia is much less than that of a background of mental retardation.

The results of our study are consistent with other previously published ones (table 4). The results of the prevalence of schizophrenia in mental retardation and the methodological details of previous studies are shown in Table 4. Thus, Penrose[6] found a prevalence of schizophrenia in patients with mental retardation of 3.7%; Leck et al.[7] of 6.2%; Reid[8-10] of 3.2%; Heaton-Ward[11] of 3.4%; Wright[14] of 1.8%; Corbett[12] of 3%; Eaton[13] of 3% and Lund[15] of 1.3% of patients with schizophrenia and 5% of unspecified psychosis. Linaker et al.[16] found 70.8% with schizophrenia among the patients with severe mental retardation, 18.7% among those with moderate retardation, 2.1% among the mild ones and 8.3% among the unspecified ones. Cowley et al.[18] performed a logistic regression analysis on a sample of 752 patients for whom they gathered a series of demographic

Table 4 Prevalence in previous studies of mental retardation and schizophrenia

Studies	Sample	Prevalence Schizophrenia in mental retardation
Penrose, 1938	Hospitalized (all ages)	3.7%
Leck et al. 1967	Hospitalized (all ages)	6.2%
Reid, 1972	Hospitalized (>16 years)	3.2%
Heaton-Ward, 1976	Hospitalized	3.4%
Corbett, 1979	n=402	3.2%
Eaton et al. 1982	Community-based program	3%
Wright, 1982	Hospitalized	1.8%
Lund, 1985	n=324 (20 a >65 years) Population with previous background and/or present one of MR by DNSMR. Registry of 22,500 persons, prevalence of MR of 0.4%.	1.3%
Linaker, 1990	Population of institutionalized patients with MR (n=168)	Severe MR: 70.8% Moderation retardation:18.7% Mild MR: 2.1% Unspecified MR: 8.3%
Cherry et al. 2000	n=60 Institutionalized. 82% Severe MR and 18% profound MR (DASH-II scale)	20 patients diagnosed of schizophrenia.

MR: Mental retardadation; DNSMR: Danish National Service for the Mentally Retarded; DASH-II: Diagnostic Assessment for the Severely Handicapped-II.

variables. In their study, they observed an increase in the incidence of schizophrenia among the patients with moderate-type mental retardation (OR = 2.24, 95% CI [1.26-4.00], $p < 0.01$).

In our study, there is an increased frequency in the diagnosis of mental retardation among the pathological backgrounds of subjects who would subsequently be diagnosed of paranoid schizophrenia and residual schizophrenia. This fact, the existence in the patients of subtle alterations in cognitive functioning in the patients already in their childhood and adolescence, would support the etiological hypothesis of the schizophrenia that involves alterations in neurodevelopment. Considered as a developmental disorder, the theory of neurodevelopment of schizophrenia means that the biological alterations of it are present at earlier ages than the characteristics of the disease that are required for its diagnosis (for example, psychosis) [34].

The subjects who develop schizophrenia in the adult age are more susceptible than healthy individuals of having suffered pre- or perinatal adverse stressants and more frequently show «minor» neurological signs and physical abnormalities, subtle indicators of an alteration in prenatal ectodermal development and minor deviations in motor, cognitive and social development[35]. The attempts to place the hypothesis of neurodevelopment into context ranges from between those who defend a «static» model of early brain lesion (pre- or perinatal)[36-37] and those who defend a latent alteration in brain maturation in the adolescence[38-39].

One limitation of the study is that the psychiatric diagnosis of psychosis and/or schizophrenia in adults is fundamentally clinical. However, at this time, the combined diagnosis based on clinical interviews and on recording data on the patients assures a better diagnosis based on the DSM-IV[40]. Another limitation is the impossibility of assuring that all the patients who form a part of the cases of our study have consulted the same site (out-patient clinics, emergencies, mental health center) and therefore, the psychiatric records may not be complete. The registry of our study is limited (between 2000 and 2004). However, this is a significant time period, considering the bibliography available. In regards to follow-up, it should be stressed that the Madrid population is characteristically stable and the population generally remains in the site of origin until well into the adult stage, which is when psychosis and/or schizophrenia becomes clinically present.

The new lines of research that can arise from the results of this study are those derived from the use of cohort studies, with their advantages and an increase in the records that we have considered in our study. In this way, prospective cohort studies with patients with and without mental retardation in the infant/childhood age would help to analyze the relationship of both cohorts with the development of schizophrenia in the adult stage.

REFERENCES

1. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987;44:660-9.
2. Amminger GP, Pape S, Rock D, Roberts SA, Ott SL, Squires-Wheeler E, et al. Relationship between childhood behavioral disturbance and later schizophrenia in the New York High-Risk Project. Am J Psychiatry 1999;156:525-30.
3. Ott SL, Allen J, Erlenmeyer-Kimling L. The New York High-Risk Project: observations on the rating of early manifestations of schizophrenia. Am J Med Genet 2001;105:25-7.
4. Goldstein G. Cognitive and perceptual differences between schizophrenics and organics. Schizophr Bull 1978;4:160-85.
5. Chapman LJ, Chapman JP. When should schizophrenic and normal groups be compared? J Psychiatr Res 1978;14:321-5.
6. Penrose LS. A clinical and genetic study of 1280 cases of mental defect. Special report of medical research council, No. 229. London: HMSO; 1938.

7. Leck I, Gordon WL, McKeown T. Medical and social needs of patients in hospitals for the mentally subnormal. Br J Prev Soc Med 1967;21:115-21.
8. Reid AH. Psychoses in adult mental defectives. I. Manic depressive psychosis. Br J Psychiatry 1972 Feb;120:205-12.
9. Reid AH. Psychoses in adult mental defectives. II. Schizophrenic and paranoid psychoses. Br J Psychiatry 1972;120:213-8.
10. Reid AH, Maloney AF, Aungle PG. Dementia in ageing mental defectives: a clinical and neuropathological study. J Ment Defic Res 1978;22:233-41.
11. Heaton-Ward A. Psychosis in Mental Handicap. The tenth Blake Marsh lecture delivered before the Royal College of Psychiatrists, February 2, 1976. Br J Psychiatry 1977;130:525-33.
12. Corbett JA. Psychiatric morbidity and mental retardation. In: James FE, Snaith RP, eds. Psychiatric illness and mental handicap. London: Gaskell Press; 1979.
13. Eaton IF, Menolascino FJ. Psychiatric disorders in the mentally retarded: Types, problems, and challenges. Am J Psychiatry 1982: 139:1297-1303.
14. Wright EC. The presentation of mental illness in mentally retarded adults. Br J Psychiatry 1982;141:496-502.
15. Lund J. The prevalence of psychiatric morbidity in mentally retarded adults. Acta Psychiatr Scand 1985;72:563-70.
16. Linaker OM, Nitter R. Psychopathology in institutionalised mentally retarded adults. Br J Psychiatry 1990;156:522-5.
17. Linaker OM, Helle J. Validity of the schizophrenia diagnosis of the psychopathology instrument for mentally retarded adults (PIMRA): a comparison of schizophrenic patients with and without mental retardation. Res Dev Disabil 1994;15:473-86.
18. Cowley A, Holt G, Bouras N, Sturmey P, Newton JT, Costello H. Descriptive psychopathology in people with mental retardation. J Nerv Ment Dis 2004;192:232-7.
19. Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch Gen Psychiatry 2003;60:709-17.
20. Stahlberg O, Soderstrom H, Rastam M, Gillberg C. Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and/or autism spectrum disorders. J Neural Transm 2004;111:891-902.
21. Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. Arch Gen Psychiatry 2000;57:1053-8.
22. Baum KM, Walker EF. Childhood behavioral precursors of adult symptom dimensions in schizophrenia. Schizophr Res 1995; 16:111-20.
23. Roff JD, Knight R, Wertheim E. A factor-analytic study of childhood symptoms antecedent to schizophrenia. J Abnorm Psychol 1976;85:543-9.
24. Roff JD. Adolescent development and family characteristics associated with a diagnosis of schizophrenia. J Consult Clin Psychol 1976;44:933-9.
25. Roff JD, Knight R, Wertheim E. Disturbed preschizophrenics. Childhood symptoms in relation to adult outcome. J Nerv Ment Dis 1976;162:274-81.
26. Done DJ, Crow TJ, Johnstone EC, Sacker A. Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. BMJ 1994;309:699-703.
27. Hodgins S, Tiihonen J, Ross D. The consequences of Conduct Disorder for males who develop schizophrenia: associations with criminality, aggressive behavior, substance use, and psychiatric services. Schizophr Res 2005;78:323-35.
28. Cannon M, Caspi A, Moffitt TE, Harrington H, Taylor A, Murray RM, et al. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. Arch Gen Psychiatry 2002;59:449-56.
29. Elman I, Sigler M, Kronenberg J, Lindenmayer JP, Doron A, Mendlovic S, et al. Characteristics of patients with schizophrenia successive to childhood attention deficit hyperactivity disorder (ADHD). Isr J Psychiatry Relat Sci 1998;35:280-6.
30. Volkmar FR. DSM-IV in progress. Autism and the pervasive developmental disorders. Hosp Community Psychiatry 1991;42:33-5.
31. Baca-Garcia E, Perez-Rodriguez MM, Basurte-Villamor I, Quintero-Gutierrez FJ, Sevilla-Vicente J, Martinez-Vigo M, et al. Patterns of mental health service utilization in a general hospital and outpatient mental health facilities: Analysis of 365,262 psychiatric consultations. Eur Arch Psychiatry Clin Neurosci 2008;258:117-23.
32. Baca-Garcia E, Perez-Rodriguez MM, Basurte-Villamor I, Fernandez del Moral AL, Jimenez-Arriero MA, Gonzalez de Rivera JL, et al. Diagnostic stability of psychiatric disorders in clinical practice. Br J Psychiatry 2007;190:210-6.
33. Baca-Garcia E, Perez-Rodriguez MM, Basurte-Villamor I, Lopez-Castroman J, Fernandez del Moral AL, Jimenez-Arriero MA, et al. Diagnostic stability and evolution of bipolar disorder in clinical practice: a prospective cohort study. Acta Psychiatr Scand 2007;115:473-80.
34. Chua SE, Murray RM. The neurodevelopmental theory of schizophrenia: evidence concerning structure and neuropsychology. Ann Med 1996;28:547-55.
35. Rapoport JL, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: update 2005. Mol Psychiatry 2005;10:434-49.
36. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987;44:660-9.
37. Gilmore JH, van TJ, Kliewer MA, Silva SG, Cohen SB, Hertzberg BS, et al. Mild ventriculomegaly detected in utero with ultrasound: clinical associations and implications for schizophrenia. Schizophr Res 1998;33:133-40.
38. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? J Psychiatr Res 1982;17:319-34.
39. Mathalon DH, Rapoport JL, Davis KL, Krystal JH. Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry. Arch Gen Psychiatry 2003;60:846-8.
40. Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S, et al. 2007 Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry 64:19-28.