Eur Arch Psychiatry Clin Neurosci (2004) 254 : 23–26 DOI 10.1007/s00406-004-0431-3

SPECIAL ISSUE

Wagner F. Gattaz · André L. Abrahão · Roberto Foccacia

Childhood meningitis, brain maturation and the risk of psychosis*

Introduction

The fact that the rate of concordance for schizophrenia among monozygotic twins is far below 100 % proves that non-genetic factors must be operant for the development or not of the disease. Such factors have frequently been discussed as related to the environment and were recently summarized elsewhere (Häfner 2002). They comprise obstetric complications, maternal psychopathology during pregnancy, intrauterine factors such as growth retardation, viruses, nutrition and low birth weight. Moreover, the risk of psychosis was also found to be influenced by factors such as urbanicity and migration, two environmental factors that are complex because they comprise a series of elements such as cultural, socioeconomic, infectious and pollution.

In spite of the heterogeneity of these risk factors, most authors agree to give them a longitudinal mode of action, emphasizing their interaction over time to increase the risk of psychosis. The environmental contribution is discussed as "something that acts continuously during most of the childhood rather than at some specific vulnerable period" (Mortensen and Pedersen, 2002), whereas Harrison and Eaton (2002) proposed a "life-course model involving multiplicative effects of provocative and protective agents across the individual's life course". Thus, there is an obvious consensus that the development or not of psychosis, and more specifically of schizophrenia, depends upon the interaction between genetic and environmental factors during the development of the brain.

W. F. Gattaz (✉) · A. L. Abrahão · R. Foccacia
Department of Psychiatry
Faculty of Medicine
University of São Paulo, Brazil
E-Mail: gattaz@usp.br

*Part of this manuscript has already been published in Häfner H (ed.) – Risk and Protective Factors in Schizophrenia. Steinkopff Verlag, Darmstadt, 2002

We will attempt to frame the contribution of the different risk factors within one model that considers schizophrenia as a disorder of brain maturation. For this, we would like to review first the concepts of synaptogenesis and synapse elimination, which are both crucial phenomena during the maturation of the brain. These data were brilliantly investigated by PR Huttenlocher and his collaborators (1982, 1984, 1987, and 1997) and will be summarized below.

Synaptogenesis and synapse elimination

Synaptogenesis in human neocortex occurs during the third trimester of gestation and during the two postnatal years. This period of intensive synaptic proliferation occurs concurrently with dendritic and axonal growth. It is then followed by a period of synapse elimination, during which synaptic density and number decrease to about 60 % of the maximum. In humans synaptogenesis and synapse elimination are heterochronous in different cortical regions. For instance maximum synaptic density in the auditory cortex is reached at age 3 months, whereas in the middle frontal gyrus at age 15 months. The end of synapse elimination in the auditory cortex is reached by age 12 years, but in the prefrontal cortex at midadolescence.

One decisive factor for the development and maintenance of synaptic connections is synaptic activity, which determines the competition for neurotrophic factors. As a simple rule, synapses that work tend to remain, those that do not, are eliminated. Thus, the input of environmental stimuli may influence the rates of synapse formation and elimination. The human brain is a product of genetic instructions, cellular interactions and influences of innate activity and external stimulation (Lagercrantz and Ringstedt 2001).

The effect of external stimulation upon activity-dependent synaptic modification has been investigated in animal experiments. O'Kusky (1985) reported that visually deprived (dark-reared) cats showed a twofold in-

crease in synaptic elimination in the visual cortex compared to normally reared cats. Similarly Meisami & Firoozi (1985) found that rats submitted to odor deprivation during the neonatal period showed in the olfactory bulb neuronal loss and permanent reduction of growth, total cell number and enzymes related to the metabolism of neurotransmitters.

These data show the profound modifications that environmental stimuli exert upon brain maturation. It is not unlikely that the interaction of the different environmental factors with the individual genetic constitution may increase the risk of schizophrenia through a disruption of the physiological process of synapse modification. Thus, it has been suggested that would the risk of psychosis would depend upon the interaction of the different factors acting continuously, rather than at some specific vulnerable period, involving multiplicative effects of provocative and protective agents across the individual's life course (Mortensen and Pedersen 2002; Harrison and Eaton 2002). Fig. 1 illustrates the effects of the different risk factors over time.

Childhood meningitis and adult schizophrenia

We would like to present now a preliminary evaluation of our data showing that a meningitis infection during childhood may increase the risk of psychosis in general, and of schizophrenia in especial during adulthood. The basis for our study was a meningitis epidemics that affected the population of São Paulo from 1971 until 1974, in which the infection rates increased from 2 cases to 170 cases per 100,000 inhabitants. Ninety percent of the infected individuals were committed to the Hospital Emílio Ribas, a 400 bed academic hospital linked to our Faculty of Medicine of the University of São Paulo.

The objectives of our study were to evaluate the lifetime psychiatric morbidity in adults infected by meningitis at age between 0–4 years, and to compare this morbidity to a control group matched by genetic and environmental (cultural, socio-economic, etc.) backgrounds. For this purpose, we chose as a control group the siblings of our subjects who had not been infected by meningitis.

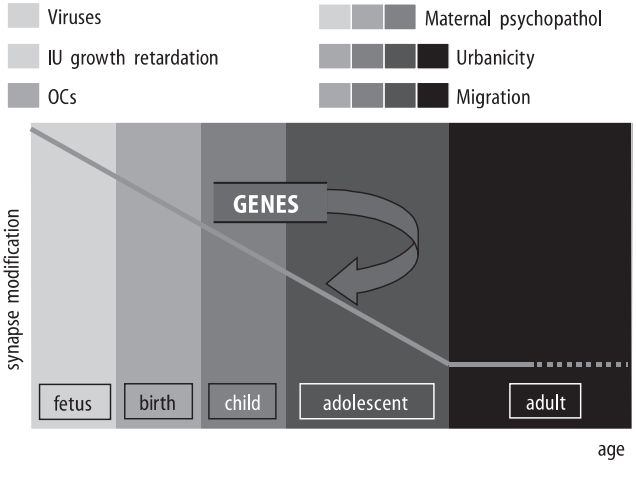

Fig. 1 Timing of environmental influences against the degree of synapse modification during the maturation of the brain. The result of the interaction between both is modulated by the genetic factors. *IU* intra-uterine; *Ocs* obstetric complications

Our database was the microfilmed medical records from Hospital Emílio Ribas, which provided us with the individual data: name, birth date, name of the parents, age at meningitis, CSF exam and duration of hospitalization. With these data a team of psychiatrists and psychologists tried to localize the individuals or their relatives through an Internet telephone directory (www.telefonica.net.br) (mean 150 calls to localize one subject).

When the subjects were localized, the following script was said to them: "Here is Dr. X, from the University of São Paulo. We are doing a research about meningitis. We would like to interview personally you and one of your siblings, with the closest age to yours. Your collaboration will be important for our study. You will receive for this interview an honorarium of R$100 to cover part of your costs."

If patients accepted, *then* we would give him the address at the *Institute of Psychiatry*. This script was made to avoid the pre-selection of a sample with an overrepresentation of psychiatric morbidity, interested in receiving priority in psychiatric care at the University Department. This bias could be expected in a city like São Paulo, in which there is a shortage of psychiatric facilities as compared to the existent need.

We found 4951 records of individuals who had a meningitis at age 4 or less. From these we searched up to now for 1745 individuals, and we found and contacted 331; from these, 173 (52 %) came to the interview, bringing with them 141 siblings without childhood meningitis. The samples were well matched regarding age, sex distribution, educational performance and IQ. The only significant difference was a higher income in the meningitis group (!) as compared to their siblings (Table 1).

All individuals underwent a semi-structured interview based on the ICD-10 Checklist (Janca and Hiller 1996), followed by a neurological exam and a neuropsychological test battery evaluating IQ, frontal function and logical memory (neuropsychological data will not be presented here).

In general, we found a similar prevalence of psychi-

Table 1 Sample description of adults infected by meningitis at age 4 years or less and their siblings without childhood meningitis infection. * $p < 0.05$

	Meningitis (n = 173)	Siblings (n = 141)
Male	77 (44 %)	50 (36 %)
Female	96 (56 %)	91 (64 %)
Age (years)	29.1 ± 1.6	30.0 ± 5.9
Years at school	11.6 ± 3.6	11.4 ± 4.0
IQ (estimated)	89.1 ± 10.4	88.8 ± 12.6
Income (R$/month)	938 ± 953	734 ± 806*

atric disorders in the meningitis (62.2 %) and the siblings (58.2 %, n. s.) groups. This prevalence is higher than that observed in a representative sample of the population from São Paulo (Andrade et al. 1999). Individuals with childhood meningitis had a 5-fold higher prevalence of psychotic disorders in general than their siblings (20.8 % vs. 4.3 %, $p < 0.001$). This difference was observed for each of the diagnoses schizophrenia, mood disorder with psychotic symptoms and 'other psychoses' (Fig. 2). No differences were found between the groups in the prevalence of the other psychiatric disorders (Anxiety, personality disorder, alcohol and drugs abuse, mood disorder without psychotic symptoms).

As expected, individuals with childhood meningitis had a higher prevalence of neurological disorders (24.8 % vs. 5.6 % in their siblings, $p < 0.001$), deafness being the most frequent (10.4 %). Because there are some studies suggesting an association between deafness and psychoses, we analyzed the data separately in individuals with and without deafness. The increased prevalence of psychoses remained in the individuals with childhood meningitis ($p < 0.001$), whereas no other difference regarding the remaining diagnoses arose. Moreover, the association between meningitis and psychoses remained significant ($p < 0.001$) when we excluded from the sample all individuals with neurological diagnoses.

The mean age at the time of the meningitis infection was 26 ± 15 months. No difference was found in the timing of the meningitis between individuals with psychosis and those without a psychiatric diagnosis (Fig. 3).

Taken together, the results from our prospective study suggest that childhood meningitis could enter the heterogeneous list of environmental factors that may increase the risk of adult psychosis (Fig. 4). All these factors may be operant at one or more levels, influencing gene expression, neuronal activity or directly synaptogenesis and synapse elimination, ending in some cases in schizophrenia. Besides the further identification of other potential risk factors, we think that our major challenge would be to identify the protective agents which, counteracting the genetic and environmental risks, would avoid or attenuate the suffering caused by a psychotic outburst.

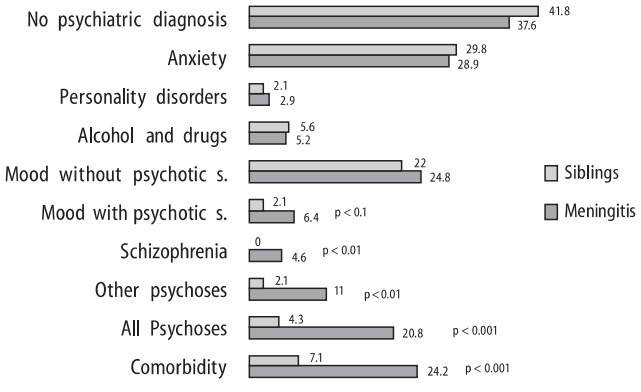

Fig. 2 Lifetime prevalence (%) if psychiatric disorders in adults infected by meningitis at age 4 years or less (n = 173) and their siblings without meningitis infection (n = 141)

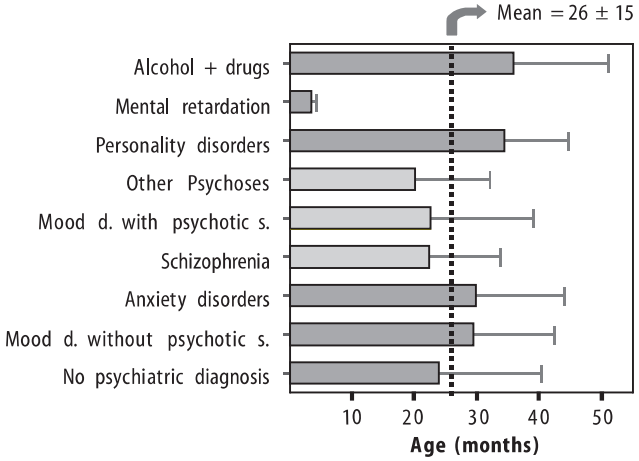

Fig. 3 Mean age at meningitis infection (in months) by diagnosis

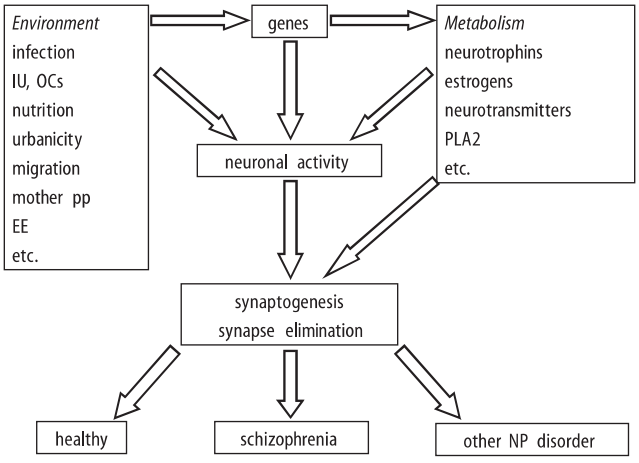

Fig. 4 Model for the effects of genetic and environmental factors on synapse modification during the maturation of the brain. Environmental factors may influence gene expression or directly neuronal activity disrupting synapse modification. Genes affect directly programmed neuronal activity or determine metabolic changes which, in turn, affect neuronal activity or synapse modification. Depending upon the degree (and probably localization) of synapse changes, an individual can develop schizophrenia or other neuropsychiatric disorders. Conversely, the interaction of these factors can have a protective effect in an individual prone to develop psychosis

References

1. Häfner H (ed) (2002) Risk and Protective Factors in Schizophrenia. Steinkopff Verlag, Darmstadt
2. Harrison G, Eaton W (2002) Migration and the social epidemiology of schizophrenia. In: Häfner H (ed) Risk and Protective Factors in Schizophrenia. Steinkopff Verlag, Darmstadt, pp 113–122
3. Huttenlocher PR, de Courten C, Garey LJ, Van der Loos H (1982) Synaptogenesis in human visual cortex – evidence for synapse elimination during normal development. Neurosci Lett 33: 247–252
4. Huttenlocher PR (1984) Synapse elimination and plasticity in developing human cerebral cortex. Am J Ment Defic 88:488–496
5. Huttenlocher PR, de Courten C (1987) The development of synapses in striate cortex of man. Hum Neurobiol 6:1–9

6. Huttenlocher PR, Dabholkar AS (1997) Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 387: 167–178
7. Lagercrantz H, Ringstedt T (2001) Organization of the neuronal circuits in the central nervous system during development. Acta Paediatr 90:707–715
8. Mortensen PB, Pedersen CB (2002) Urban/rural life as a risk factor. In: Häfner H (ed) Risk and Protective Factors in Schizophrenia. Steinkopff Verlag, Darmstadt, pp 123–131
9. O'Kusky JR (1985) Postnatal changes in the numerical density and total number of asymmetric and symmetric synapses in the hypoglossal nucleus of the rat. Brain Re Dev Brain Res 108: 179–191
10. Meisami E, Firoozi M (1985) Acetylcholinesterase activity in the developing olfactory bulb: a biochemical study on normal maturation and the influence of peripheral and central connections. Brain Res 353:115–124
11. Janca A, Hiller W (1996) ICD-10 Checklists – a tool for clinicians' use of the ICD-10 classification of mental and behavioral disorders. Comprehensive Psychiatry 37:180–187
12. Andrade LHSG, Lólio CA, Gentil V, Laurenti R (1999) Epidemiologia dos transtornos mentais em uma área definida de captação da cidade de São Paulo, Brasil. Rev Psiq Clin 26:257–261. Also available in http://www.hcnet.usp.br/ipq/revista/r265/artigo(257).htm