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Plasma pterins and folate in late life depression: The Rotterdam Study

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Abstract

Tetrahydrobiopterin is a cofactor in the synthesis of monoamine neurotransmitters. High neopterin levels generally signal increased immune activation. Both pterins have been investigated in several small clinical studies of depressed patients with conflicting results. Therefore, we examined the relation of plasma biopterin and neopterin with depression in a population-based study. We also studied the association of pterins with folates in depressed persons as this vitamin is required for pterin biosynthesis. We screened 3884 adults aged 60 years and over for depressive symptoms. Screen positive subjects had a psychiatric interview to diagnose DSM-IV disorder. Plasma pterins and serum folate were determined in all persons with depressive symptoms ($n=238$) and randomly selected non-depressed persons ($n=357$). We found no association between the concentration of biopterin or neopterin with depressive symptoms or depressive disorders. However, in depressed persons the relation between pterins and folates was different than in the non-depressed, i.e. neopterin concentrations increased with folate levels in persons with depressive symptoms (0.09 per log(nmol/l folate); 95% CI=0.01, 0.18, $P=0.03$), but not in non-depressed persons (−0.07 per log(nmol/l folate); 95% CI=−0.17, 0.03, $P=0.18$). The interaction between depressive symptoms, folate and neopterin was significant ($P=0.03$). The study suggests that the relation between folate and pterins is altered in the depressed elderly.

Keywords: Depression; Folates; Pterins; Population-based; Elderly; Monoamine synthesis

1. Introduction

Biopterin and neopterin are endproducts of different pathways of the pterin metabolism. The best-established function of the biologically active biopterin, tetrahydrobiopterin (BH_4), is that of a cofactor in the hydroxylation of phenylalanine, tyrosine and tryptophan (Thony et al., 2000). These are rate-limiting steps in the synthesis of the monoamine neurotranmitters dopamine, serotonin and noradrenaline. In addition to the hydroxylation of aromatic amino acids, BH_4 serves as a cofactor for enzymes such as nitric oxide synthase and glycerol-ether monooxygenase (Blau et al., 2001).

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Changes in BH_4 metabolism can be assessed by measurement of total biopterins and neopterin. Experimental studies suggest that a raised neopterin/biopterin ratio may indicate a failure to synthesize BH_4 (Barford et al., 1984; Thony et al., 2000). However, neopterin is released by activated macrophages and also considered a marker of cell-mediated immunity and oxidative stress (Murr et al., 2002). Hence, pterins can be linked to depression via the monoamine and the immune system as both are implicated in the pathophysiology of depression. Biological research among depressed patients focused on the dysregulation of neuroendocrine and neurochemical systems. However, there is also good evidence that depression is accompanied by multiple impairments of the immune system (Zorrilla et al., 2001). Within the neurochemical systems, the neurotransmitters serotonin, norepinephrine, dopamine, glutamate and GABA are particularly implicated in the pathophysiology of mood disorders (Ordway et al., 2002). According to the monoamine hypothesis, depression is due to a deficiency of serotonin or noradrenaline (van Praag, 1982). It is widely held that most antidepressants have their effect by modulating the monoamine system but attempts to evaluate the neurochemical pathology of the monoamine systems have led to diverse findings and suggest interaction with other neurotransmitters and hormones.

Against this background, several small clinical studies have tried to relate plasma concentrations of total biopterin, BH_4, or neopterin to depressive disorders in patients (Hashimoto et al., 1987, 1988; Knapp and Irwin, 1989; Hashimoto et al., 1990; Hoekstra et al., 2001). In other studies, urinary excretion of total biopterin was assessed (Coppen et al., 1989; Abou-Saleh et al., 1995). The differences in analytical method and setting make the studies hard to compare and could explain the conflicting findings. Reduced and increased concentrations of biopterin in depressed patients have been reported. More recently, the relation of folates with pterins was investigated as an indicator of changes in BH_4 metabolism (Abou-Saleh et al., 1999; Bottiglieri et al., 2000). Folate is required to form the starting molecule, guanosine triphosphate, of the pterin biosynthesis. Moreover, a salvage pathway for BH_4 depends on dihydrofolate reductase although non-folate dependent regeneration pathways may be more important in humans (Hamon et al., 1986; Thony et al., 2000). It has been suggested that impaired synthesis of BH_4 due to folate deficiency explains the association between folates and affective disorders. On the other hand, oxidative stress and immunological processes can affect both folate and pterin metabolism (Widner et al., 2002).

The aim of this study was to investigate both the relation of biopterin and neopterin with depression in a large population-based sample of older adults, and the association of folate concentrations with pterins in the depressed and non-depressed elderly.

2. Methods

2.1. Study population

This study is based on the third examination round of the Rotterdam Study, an ongoing population based cohort study in a district of Rotterdam (Hofman et al., 1991). The Medical Ethics Committee of the Erasmus University approved the study and written informed consent was obtained from all participants after the nature of the procedures had been fully explained. Measurements took place between March 1997 and December 1999 and included a home interview and a visit to the research center. Of the 4703 persons over 60 years who participated in the home interview, 3884 visited the research center, where blood was drawn. The 819 subjects who were not seen at the center were on average older (77.5 vs. 72.3 years), more likely to be female (70% vs. 58%) and had more depressive symptoms (12.2% vs. 6.8%, overall prevalence 7.8%). From 3510 subjects, blood samples were available for biochemical analysis. The 334 subjects in whom no or insufficient blood samples were available did not differ from the remainder in respect to age, gender and frequency of depressive symptoms. In the present analysis, we compared plasma biochemical parameters between all non-demented subjects with depressive symptoms and 357 randomly selected non-demented reference subjects (see Section 2.3).

2.2. Depression assessment

Depressive disorders were assessed by using a two-step procedure. First, participants completed the Dutch version of the original Center for Epidemiologic Studies Depression scale (CES-D) during the home interview. The CES-D is a 20-item self-reported measure of symptoms experienced in the past week including a question on lack of appetite. Each item is scored on a scale of 0 to 3 points. The criterion validity of the CES-D version is well established (Sawyer-Radloff, 1977). We used a score of 16 as a cut-off, and this score had a very high sensitivity for major depression in elderly subjects in the Netherlands (Beekman et al., 1997). Moreover, previous studies have verified that a score of 16 and above on the CES-D represents clinically