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(54) **CSF DIAGNOSTIC IN VITRO METHOD FOR DIAGNOSIS OF DEMENTIAS AND NEUROINFLAMMATORY DISEASES**

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(57) **ABSTRACT**

CSF diagnostic in vitro method for the diagnosis of dementias and neuroinflammatory diseases, in which a determination of the procalcitonin immunoreactivity (PCT immunoreactivity) is carried out in a sample of cerebrospinal fluid (CSF) of a patient who is suffering from a dementia or neuroinflammatory disease or is suspected of suffering from such a disease. Conclusions about the presence, the course, the severity or the success of a treatment of the dementia or neuroinflammatory disease are drawn from a measured PCT immunoreactivity which is above a threshold value typical for healthy individuals.

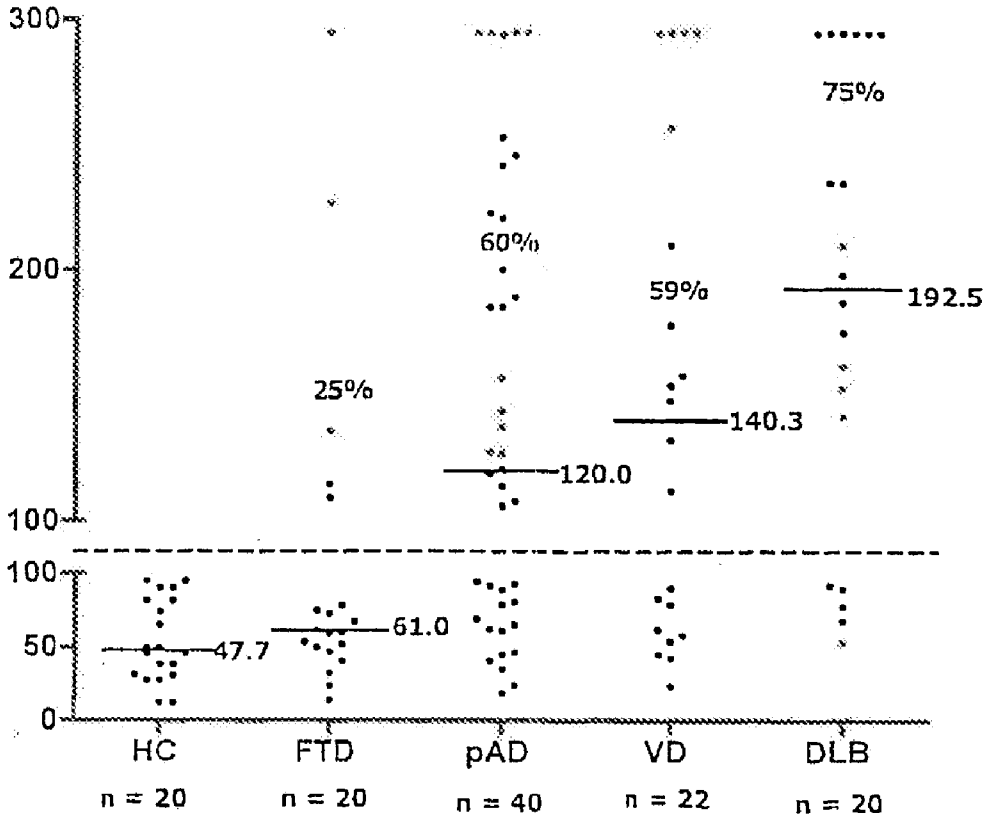
300
200
100
100
50
0
75%
60%
59%
192.5
25%
140.3
120.0
61.0
47.7
HC
FTD
pAD
VD
DLB
n = 20
n = 20
n = 40
n = 22
n = 20

FIGURE 1

CSF DIAGNOSTIC IN VITRO METHOD FOR DIAGNOSIS OF DEMENTIAS AND NEUROINFLAMMATORY DISEASES

[0001] The present invention relates to a novel CSF diagnostic in vitro method for diagnosis of dementias and neuroinflammatory diseases.

[0002] In the context of the present invention, the term "diagnosis" is used as a general term for medical determinations which, depending on the clinical state of the patient for whom the determination is carried out, may be based on different problems and which serve in particular for detection and early detection, determination of severity and monitoring, including monitoring during the treatment, and prognosis of the future course of the disease.

[0003] The method according to the invention is a CSF diagnostic in vitro method. A CSF diagnostic method is understood as meaning a method which is usually carried out in the course of the diagnosis of neurological diseases and in which the determination of a property of the so-called cerebrospinal fluid (CSF) which is informative for diagnostic purposes is effected. In the case of the present invention, the specific property is the immunodiagnostically determinable content of a biomolecule in the CSF.

[0004] The diseases which are diagnosed according to the present invention are in particular presenile dementias, as will be discussed in more detail in the present Application, and further chronic neuroinflammatory diseases of non-infectious aetiology.

[0005] Dementias are generally defined as diseases for which a common feature is the loss of acquired intellectual capabilities, especially of the memory, and of the normal level of the personality as a consequence of brain damage. Dementias are as a rule relatively slowly developing diseases of chronic character. If dementia phenomena occur before old age, in middle aged people, they are referred to as presenile dementias and, on the basis of the symptoms typical of them and pathological changes in the brain, a differentiation is made in particular between the following four diseases or groups of diseases:

[0006] Alzheimer's dementia (AD) (Alzheimer's disease) is the most frequent neurodegenerative dementia and accounts for ⅔ of all cases of dementia. AD is distinguished by three important pathological features: the formation of amyloid plaques and neurofibrillar bundles and the loss of nerve cells (for an overview, cf. 24; references in the description in the form of numbers refer to the list of references following the description). Amyloid plaques consist of extraneuronal aggregates of amyloid-β-protein, while the neurofibril bundles contain mainly tau-protein and neurofilaments. It is presumed that the plaque and neurofibril formation is the cause of the death of nerve cells.

[0007] The most important symptoms of AD are increasing dysfunctions of memory and intellect with relatively persistent emotional responsiveness, these symptoms being accompanied by further less specific disturbances which make it difficult to differentiate AD from other forms of dementia.

[0008] Dementia with Lewy bodies (DLB) is the second most frequent cause of a dementia after Alzheimer's dementia (11; 18). Neuropathologically, DLB is characterized by the occurrence of so-called Lewy bodies in the brain stem and in the cortex. These Lewy bodies consist predominantly of aggregates of the presynaptic protein (α-synuclein) and ubiquitin. Lewy body pathology can be associated to different extents with neuropathological changes typical of Alzheimer's and Parkinson's disease. Thus, in DLB too, the formation of β-amyloid and senile plaques occurs, but not neurofibril bundles (for an overview, cf. 6) . Lewy bodies are also present in the brain of patients with Parkinson's disease, even if in a different distribution (for an overview cf. 19).

[0009] Key symptoms of DLB are a progressive cognitive disturbance, episodes of confusion with fluctuating attention and consciousness, Parkinsonism, frequent falls and syncopes (brief, paroxysmal unconsciousness) (17). The sensitivity and specificity of the diagnostic criteria (17) show high specificity throughout but a very low sensitivity in some cases. This means that DLB is frequently not diagnosed in clinical routine. In particular the differentiation from Alzheimer's disease must be further improved.

[0010] Frontotemporal dementia (FTD) is also referred to as Pick's disease and accounts for about 20% of presenile dementias. FTD is genetic in some cases and is among the so-called tauopthies, which are distinguished by overexpression or underexpression of a tau-protein subtype (34) or by the expression of a mutated tau-protein (23). Neuropathological symptoms are local atrophy of the frontal and/or temporal cortex and of the substantia nigra and of the basal ganglia. This results in different levels of speech disturbance, a change of personality and behavioural peculiarities. Overall, FTD is underdiagnosed with a sensitivity of 93% and a specificity of only 23%, AD being the most frequent misdiagnosis (30).

[0011] The term vascular dementia (VAD) covers diseases in which a dementia is triggered owing to disturbed blood flow in the brain. There are different types of VAD, of which multi-infarction dementia (MID) and subcortical VAD (also referred to as Binswanger's disease) are the most frequent forms.

[0012] Binswanger's disease is a slowly progressing dementia which is characterized pathologically by cerebrovascular lesions in the white brain substance. Clinically this results in behavioural peculiarities, such as agitation, irritability, depression and euphoria, and slight memory disturbance (4).

[0013] Multi-infarction dementia arises gradually as a consequence of several small strokes, also referred to as transient ischaemic attacks (TIA), which led to the destruction of brain tissue in the cortex and/or subcortical areas (9). The strokes may also have remained completely unnoticed, in which case the dementia is the first noticeable consequence. In the presence of MID, there is a gradual decrease in cognitive capabilities, associated with severe depressions, mood fluctuations and epilepsy.

[0014] A diagnosis of dementias is performed nowadays predominantly on the basis of neuropsychological investigations and the observation of the development of the disease and its course using exclusion criteria for certain forms of dementia. In very many cases, these investigations give ambiguous results, which explain the abovementioned numbers for the underdiagnosed forms of dementia or incorrectly diagnosed cases. The cerebral changes typical of the disease cannot of course be established directly in living patients and technical medical investigations of brain function by means of, for example, X-ray tomography or MRI are complicated and expensive.

[0015] There is a need for supplementary methods of investigation which permit diagnosis of dementia and which facilitate in particular the differentiation of different forms of

dementia with similar or blurred clinical symptoms, an immunodiagnostic determination of biomarkers of a suitable specificity and sensitivity being particularly desirable.

[0016] The present invention provides such a method of investigation in the form of a CSF diagnostic in vitro method for detection and early detection, for the determination of severity and for monitoring and prognosis of dementias and neuroinflammatory diseases according to claim **1**, in which a determination of the procalcitonin immunoreactivity (PCT immunoreactivity) is carried out in a sample of the cerebrospinal fluid (CSF) of a patient who is suffering from a dementia or neuroinflammatory disease or is suspected of suffering from such a disease, and conclusions about the presence, the type, the course, the severity or the success of a treatment of the dementia or neuroinflammatory disease are drawn from a measured PCT immunoreactivity, which is above a threshold value typical for healthy control persons.

[0017] In particular, the PCT determination in the CSF is effected, as emphasised in claim **2**, with the aid of a highly sensitive PCT immunoassay having a functional assay sensitivity (FAS) of better than 100 ng of PCT per 1 (100 ng/l or 100 pg/ml), in particular better than 50 ng/l and particularly preferably better than 10 ng/l.

[0018] Advantageous developments of the method according to claims **1** and **2** are described in subclaims **3** to **12**.

[0019] Since the measurements described in more detail below have shown that the PCT immunoreactivity in CSF can be measured with high precision and reliability by a highly sensitive immunoassay having a functional assay sensitivity (FAS) which is considerably better than that of the commercial PCT immunoassays available for sepsis diagnosis, while—as will be explained below—the isolated attempts to date with regard to a PCT determination in CSF by the known assays led to contradictory results providing little information, the invention also relates, according to claim **13**, very generally to the use of a highly sensitive immunoassay for procalcitonin determination having a functional assay sensitivity (FAS) of 50 ng/l or better, in particular of 10 ng/l or better, for the determination of procalcitonin immunoreactivity in cerebrospinal fluid (CSF).

[0020] Functional assay sensitivity (FAS; also functional inter assay sensitivity) is defined as a parameter which indicates the analyte concentration which is measured by the respective method with an interassay precision (an interassay coefficient of variation) of ≦20% (35).

[0021] The present invention is based on considerations by the inventors for improving the diagnosis of dementias and in particular the differential diagnosis for distinguishing between different forms of presenile dementia by applying the discovery that the known forms of presenile dementia explained in more detail at the outset are also accompanied—to different extents—by inflammatory processes which are regarded as essential for the development, the symptoms and the course of dementias.

[0022] Thus, Alzheimer's disease is characterized, inter alia, by the occurrence of chronic local inflammatory reactions in the brain with participation of various inflammatory proteins, such as complement factors, acute-phase proteins and proinflammatory cytokines (1, 30).

[0023] Inflammatory processes also play a role in the origin of vascular dementias (VAD). The levels of TNFα, TGFβ, IL-6 and GM-CSF (granulocyte-macrophage colony-stimulating factor) are substantially elevated in patients with VAD (28; 29).

[0024] It is presumed that both in the case of AD and in the case of VAD a similar cytokine production cascade is started as a response to neuronal damage, although the triggering factors of these two forms of neurodegeneration are different and lead to different neuropathological changes in the brain (28).

[0025] In DLB, too, inflammatory processes appear to play a role. Thus, the number of activated microglia cells in the brain of patients with DLB is increased (15), and proinflammatory cytokines, such as TNFα, are overexpressed in certain regions of the brain, such as the amygdala and the hippocampus (13).

[0026] There are only sparse indications for the occurrence of inflammatory reactions in the brain of FTD patients. In a study by Sjogren et al., it was possible to measure significantly elevated concentrations of the pro-inflammatory cytokine TNFα and of the anti-inflammatory cytokine TGFβ in the cerebrospinal fluid of some FTD patients (26).

[0027] Against a background of extensive clinical material and extensive experience on the part of the Applicant which relates to the occurrence of the peptide procalcitonin (PCT) in the serum and plasma of sepsis patients and other patients, the inventors thought it a worthwhile problem to determine whether changes of PCT concentrations which can be related in a diagnostically relevant manner to dementias and other neuroinflammatory diseases can be determined in the CSF.

[0028] Procalcitonin (PCT) is a peptide which consists of 116 amino acids and was first discussed as a precursor of the important hormone calcitonin (thyreocalcitonin) and the complete amino acid sequence of which has been known just as long as the details of its proteolytic degradation which leads to the liberation of the mature hormone calcitonin and other shorter peptides, including in particular so-called katacalcin (procalcitonin 96-116) and an n-terminal peptide (n-procalcitonin 1-57), which are abbreviated herein to "PCT partial peptides". As explained in more detail, for example, in the patents EP 0 656 121 B1 and U.S. Pat. No. 5,639,617 and in (2), severe bacterial inflammations with systemic reaction result in the release of PCT into the circulation where it is found in very high, readily measurable amounts (2; cf. also the overviews in 22; 33; 3). Reference is made expressly to the general technical knowledge recorded in said patents and references for supplementing the present description. Viral, autoimmune and allergic diseases on the other hand do not lead to a significant increase in the PCT concentration in the blood. PCT reflects the severity of a bacterial infection and is used as a marker for the diagnosis and therapeutic monitoring of sepsis, severe sepsis and septic shock (5; 7; 27; 32; 21).

[0029] The determination of PCT may also be used for differential diagnostic purposes since inflammatory diseases of infectious aetiology can be distinguished from those of non-infectious aetiology on the basis of the measurable PCT concentrations in serum and plasma (cf. also EP 0 880 702 B1).

[0030] PCT is determined, as described in the abovementioned patents and references, in a suitable manner by immunoassays of the sandwich type using two antibodies which bind to the amino acid sequence of the complete PCT peptide so that the PCT processed completely with release of calcitonin is not detected but the total unprocessed PCT and optionally also those longer PCT partial peptides which have both binding sites for the antibodies used in the assay are detected. Since the sandwich assays used do not as such detect exclusively the complete unprocessed PCT, it is preferred in the present application to refer to the determination of a PCT immunoreactivity instead of a PCT determination, with the result that the appearance of a stipulation for an exclusive measurement of a molecule with the complete PCT sequence is to be avoided. In general, the measurement of the PCT immunoreactivity can be designated as a measurement

by a sandwich immunoassay using two antibodies which bind to those segments of the complete PCT peptide which, in the proteolytic processing of PCT with formation of calcitonin, are located on different members of the PCT partial peptides formed or which are located on PCT partial peptides which do not comprise the calcitonin sequence.

[0031] The fact that it is not the complete PCT 1-116 which is determined in serum or plasma in the case of sepsis but a PCT 3-116 shortened by two amino acids is explained in EP 1 121 600 A1 and EP 1 48 334 A1 or U.S. Pat. No. 6,756,483, which are referred to for supplementing the present description.

[0032] For the determination of the procalcitonin immunoreactivities in serum/plasma, there exists, for example, the commercial chemiluminescence assay LUMItest® PCT (B.R.A.H.M.S. AG), which has a functional assay sensitivity (FAS) of 300 ng/l and is tailored to PCT determination in sepsis, where very high PCT concentrations can occur. For PCT determination with a higher sensitivity, a modified sandwich immunoassay which operates with an affinity-purified polyclonal antibody and which is described in more detail in (20) and is obtainable as LUMItest® PCTsensitiv (B.R.A.H.M.S AG) was recently developed. This assay has a clearly better FAS of 7 ng/l (20). With the aid of this assay, it was possible to determine a mean PCT serum concentration of 13.5 ng/l (13.5 pg/ml) in healthy persons, values from <7 to 63 ng/l having been found and the 97.5% percentile being 42.5 ng/l.

[0033] Data on experiments to measure PCT in CSF too, appear only sparsely in the scientific literature, and all measurements described were carried out under premises which cannot be logically related to the determination, according to the invention, of PCT in CSF for the diagnosis of dementias and further neuroinflammatory diseases:

[0034] Starting from the suitability of PCT as an infection marker, an attempt was made to determine whether PCT concentrations in the CSF of patients with meningitis (8; 12; 25) or Lyme borreliosis (14) are measurable and may permit a distinction between bacterial meningitis and viral meningitis. The findings were contradictory, either no increased measured values at all being obtained (8; 25) or only a weak indication being possible (12).

[0035] Starting from a genetic relationship between PCT and the peptide CGRP (calcitonin gene related peptide) and homologous sequence designations for adrenomedullin (ADM), which was measured at elevated levels in the CSF of children with traumatic brain injury (TBI), it was furthermore investigated whether elevated PCT concentrations can be found in the CSF in the case of such children too (10). There, it was possible to find elevated PCT concentrations, which were related to an acute-phase reaction to the trauma, even if the significance of the observations as a whole remained unclear. It is not possible to find any recognizable logical relationship with measurements in the case of dementias and further neuroinflammatory diseases which form the subject of the present invention.

[0036] In all cases where an attempt was made to determine PCT in the CSF, the commercial assay developed for sepsis diagnosis in serum or plasma, which had an FAS of only 300 ng/l, was employed.

[0037] The Applicants have reason to assume that considerably improved measured results with better diagnostic significance are obtained in the CSF also in the case of, for example, infectious diseases, such as bacterial meningitis, if measurements as described, for example, in (8; 12) are carried out by a highly sensitive PCT assay according to (20), as was used in the case of the measurements which form the basis of the present invention and are described in the experimental section. It should be pointed out that clear standard concentrations for healthy persons could be determined by such a highly sensitive assay under the conditions described. The present application therefore furthermore relates very generally to the measurement of PCT in the CSF by a highly sensitive immunoassay for diagnostic purposes.

[0038] Below, the invention is explained in more detail with reference to measured results and a figure.

[0039] FIG. **1** shows the results of the measurement of the PCT immunoreactivity in the CSF of healthy normal persons (HC) and in the CSF of patients with four different diagnosed types of presenile dementias, namely frontotemporal dementia (FTD), Alzheimer's dementia (pAD), vascular dementia (VAD) and dementia with Lewy bodies (DLB), and with the median concentrations and sensitivities for the individual forms of dementia for the measured groups of patients.

EXPERIMENTAL SECTION

Description of Assay

[0040] The measurement of procalcitonin in the cerebrospinal fluid was effected as described in (20). However, the lyophilised standards were dissolved not in zero serum but in PBS (with 1% BSA).

Measurement of the PCT Immunoreactivity in the Cerebrospinal Fluid of Healthy Controls and Patients with Presenile Dementias

[0041] Procalcitonin was detected with the LUMItest® PCTsensitiv (cf. 20) in cerebrospinal fluid of healthy control persons. It was possible to show that the concentrations are in the range between 12 and 133 ng/l (median concentration 50 ng/l). Since the median PCT concentration in the serum of healthy persons was determined only as 13.5 ng/l (20), there is a PCT concentration gradient between blood and CSF of about 1:4 in healthy persons.

[0042] The measured PCT concentrations in the cerebrospinal fluid of healthy controls and patients with different forms of presenile dementia are shown in FIG. **1**.

[0043] The respective sensitivity and specificity of the highly sensitive LUMItest® PCTsensitiv assay for the diagnosis of different presenile dementias are shown in table 1.

TABLE 1

Specificity and sensitivity of the measurements of the PCT immunoreactivity in the CSF of patients with different dementias

Dementia	Specificity (%)	Sensitivity (%)
Subjective cognitive disturbances	100	50
Frontotemporal dementia	100	25
Alzheimer's dementia*	100	60
Vascular dementia	100	59
Dementia with Lewy bodies	100	75

Group of patients diagnosed with "probable Alzheimer's disease" (pAD), the diagnosing institution having a mean statistical reliability for Alzheimer diagnosis of 90%.

[0044] According to FIG. **1**, the measured results show different median concentrations for the different patient groups, the group of FTD patients (patients with subjective cognitive disturbances) giving on average only slightly higher measured values than healthy persons and differing substantially from the other patient groups in whom the mean PCT concentrations (i) were considerably elevated compared with

healthy persons, and (ii) also differed from group to group. DLB patients had the highest measurable PCT concentrations and were found to be positive with a high sensitivity of 75% (within the clinically presorted groups; specificity 100%).

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1. A CSF diagnostic in vitro method for detection, determination of severity and monitoring and prognosis of dementias and neuroinflammatory diseases, wherein a determination of the procalcitonin immunoreactivity (PCT immunoreactivity) is carried out in a sample of the cerebrospinal fluid (CSF) of a patient who is suffering from a dementia or neuroinflammatory disease or is suspected of suffering from such a disease, and conclusions about the presence, the course, the severity or the success of a treatment of the dementia or neuroinflammatory disease are drawn from a measured PCT immunoreactivity which is above a threshold value typical for healthy control persons.

2. The method according to claim **1**, wherein the PCT immunoreactivity is determined with the aid of a highly sensitive PCT immunoassay having a functional assay sensitivity (FAS) of better than 100 ng of PCT per 1 (100 ng/l or 100 pg/ml), preferably better than 10 ng/l.

3. The method according to claim **1**, wherein an average value which is determined for healthy control persons and is about 50 pg/ml is used as a threshold value for the diagnosis "suspicion of neuroinflammatory disease".

4. The method according to claim **1**, wherein the PCT immunoassay for measurement of the PCT immunoreactivity is a sandwich immunoassay using two antibodies which bind to those segments of the complete PCT peptide which are located on different members of the PCT partial peptides formed in the proteolytic processing of PCT with formation of calcitonin or which are located on PCT partial peptides which do not comprise the calcitonin sequence.

5. The method according to claim **4**, wherein one of the antibodies binds to a segment of the calcitonin sequence and the other of the antibodies binds to a segment of the katacalcin sequence, and in that at least one of the two antibodies is an affinity-purified polyclonal antibody.

6. The method according to claim **1**, wherein the dementia is a presenile dementia selected from the group consisting of Alzheimer's dementia (AD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD) and various forms of vascular dementia (VAD), and in that the method is carried out as part of differential diagnosis.

7. The method according to claim **6**, wherein the method is carried out as a differential diagnostic method in which the measured PCT immunoreactivity values are related to value ranges typical for the individual forms of dementia and a probability of the presence of one of the possible forms of dementia is determined.

8. The method according to claim **1**, wherein the neuroinflammatory disease is a chronic neuroinflammatory disease of non-infectious aetiology.

9. The method according to claim **1**, wherein said method is carried out as part of a multi-parameter determination in which at least one further biochemical or physiological parameter informative for the respective clinical picture is simultaneously determined and in which the measured result is obtained in the form of a set of at least two measured variables which is evaluated for the fine diagnosis of dementia or neuroinflammatory disease.

10. The method according to claim **9**, wherein, as part of the multi-parameter determination, in addition to the PCT immunoreactivity, at least one further inflammation mediator is determined which is selected from the group consisting of complement components, cytokines, chemokines, blood coagulants and fibrinolytic factors, acute-phase proteins and free radical compounds.

11. The method according to claim **9**, wherein the multi-parameter determination is carried out as a simultaneous determination by means of a chip technology measuring apparatus or an immunochromatographic measuring apparatus.

12. The method according to claim **9**, wherein the evaluation of the complex measured result of the multi-parameter determination is effected with the aid of a computer program.

13. (canceled)

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