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Treatment resistance in major depression is correlated with increased plasma levels of neurofilament light protein reflecting axonal damage

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A B S T R A C T

Treatment resistant major depression is accompanied with a sizable impact on quality of life with severe consequences for social integrity, individual health and socioeconomic state. In- and outpatient care of patients with treatment resistant major depression remains very challenging for both patients and the health system. One reason is the limited knowledge on the etiology of treatment resistance in major depression resulting difficulties developing efficient treatment strategies for this group of severe depressed patients. Therefore, new focuses on research are needed. Biomarkers reliably reflecting neuropathological processes could help to understand the actual mechanisms in treatment resistance. Neurofilament light protein might be a reliable biomarker of axonal damage in the brain. Due to accumulating evidence that major depression is associated with axonal damage, it is our hypothesis that treatment resistant major depression is correlated with persistent axonal damage within circuits processing affective responses. Axonal damage is reflected by increased levels of neurofilament light protein in plasma. To evaluate our hypothesis, neurofilament light protein will be measured in a group of patients with homogeneous symptomatology of treatment resistant major depression.

Introduction

Despite sizable efforts and developments in research on the neurobiology of depression we still don‘t know its exact underlying pathophysiology. Recently, promising results about its etiology were published. Specifically, neuroinflammation and genetics were dominating themes in psychiatric research. Regarding the vast effort in these fields significant diagnostic and new effective treatment outcomes are minimal or more precisely still missing. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study one third of the patients with an initial and acute antidepressant therapy with citalopram reached remission during 12–14 weeks of treatment only. After all sequenced treatment alternatives in this study including treatment with cognitive therapy and different classes of antidepressants, either alone or combined with a second antidepressant or augmented (lithium or triiodothyronine, liothyronine) only 67% of the patients remitted [1]. In case of failure of several courses of antidepressant medications in most instances the next step is treatment with electroconvulsive therapy (ECT). Electroconvulsive therapy is an effective short-term treatment for depression [2]. Its response rates are estimated to be within 80–90% when used as a first line treatment or in case of inadequate pharmacotherapy before ECT. Patients who have failed to one or more adequate trials with antidepressant medications seem to have lower response rates of an estimated 50–60% [3]. However, there remains a group of so far treatment resistant depressed patients who do not benefit from established antidepressant therapies like psychopharmacology, psychotherapy or even electroconvulsive therapy. Regarding the sizable burden that depression means both for affected individuals and their social environment it is crucial that we need new focus as well as innovations in research on recurrent but also in treatment resistant depression.

In addition to the lack of knowledge on neurobiological mechanisms of recurrent depression we know even less about the putatively distinct mechanisms of treatment resistance. Due to new imaging techniques and neuromodulatory interventions like deep brain stimulation mood disorders are commonly regarded as dysfunctions of neural networks [4,5]. One important substrate of neural networks is the axon. There is evidence that major depressive disorder (MDD) might be associated with axonal damage [6]. Today one is able to detect correlates of axonal damage via a specific biomarker named neurofilament light protein (NF-L) [7]. Neurofilament light protein is an abundant part of the axonal cytoskeleton and can be released into the cerebrospinal fluid following axonal damage [8,9]. Recent technological advancements enable its determination in very low concentrations not only in cerebrospinal fluid but also in plasma [10]. Plasma levels of neurofilament light protein have already been discussed as a reliable biomarker in neurological and neurodegenerative diseases, we believe that they play the same role in treatment resistant affective disorders.

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The hypothesis

Treatment resistant major depression is associated with persistent axonal damage affecting proper transmission within circuits regulating mood. This axonal damage in treatment resistant major depression is reflected by significantly increased plasma levels of neurofilament light protein in comparison to healthy persons as well as in comparison euthymic patients with episodic major depression.

Axonal damage in major depression

If indeed axonal damage plays a role in treatment resistant major depression, this begs the question what its exact mechanisms are. Many studies have shown hippocampal volume reductions in major depression [11]. It is a widely hold tenet that this volume reduction associated with depression is due to neuronal loss or decreased neurogenesis [30]; however, it is very likely that alterations in glial cells or neuropil rather than neuronal loss or decreased neurogenesis play a key role in this process [12–14]. In this context, there is growing evidence not only for an abnormal myelin content in the whole brain but also an involvement of myelin pathologies in major depression [15–17]. Myelin pathologies like alterations of oligodendrocyte structure and function are thought to have a key impact on axon-myelin interactions directly influencing conduction velocity and axonal integrity [6,18,19]. Disruptions of axon-myelin adhesion can lead to axonal damage through alterations of the axonal cytoskeleton [20].

Further evidence implicating axonal damage in major depression is brought to the table by decreased fractional anisotropy in diffusion tensor imaging in the genu of the corpus callosum in subjects with major depression [21]. Diffusion tensor imaging is a technology of in vivo structural imaging being able to track nerve fiber bundles in white matter quantifying water diffusion by fractional anisotropy. Fractional anisotropy is a measure of how diffusion is directionally hindered. Although the dense packing of axons and their axonal membrane plays the primary role in fractional anisotropy myelination is able to modulate its degree [22].

The evidence for axonal damage in major depression from animal, human and postmortem studies is compelling and leads to the hypothesis that treatment resistance is associated with persistent axonal damage within neural networks involved in processing affective stimuli.

Neurofilament light protein

The cellular extensions of neurons called axons allow transmission of both electric and chemical signals to other neurons make up the extremely complex and highly functional network of the brain, the most complex structure known to man. Neurons and their axons contain proteins building a filamentous network to form the cytoskeleton, which provides the neuronal cytoarchitecture and contributes to intracellular transport function. Three cytoskeleton components are differentiated according to their size, the microfilaments, intermediate filaments and microtubules. In addition to their size difference they are differentially distributed in neurons and axons. With a diameter of 10 nm, the intermediate filaments are midway in size between smaller microfilaments (6 nm) and bigger microtubules (23 nm). The intermediate filaments comprise six (I–VI) different classes and are expressed cell-specifically. Class IV of the intermediate filaments is expressed in neurons and composed of neurofilament heavy protein (NF-H, 200–220 kDA), neurofilament medium protein (NF-M, 145–160 kDA), neurofilament light protein (NF-L, 68–70 kDA) and alpha-internexin (58–66 kDA). Neurofilament light proteins are abundant in axons and are germane to radial growth and conduction velocity [8,9,23,24]. Axonal damage due to all influences possible leads to neurofilament light protein release into the extracellular compartment. By diffusion into the cerebrospinal fluid (CSF) it gets measurable in CSF by using immunoassays [8,9]. Thanks to the development of a single-molecule enzyme-linked immunosorbent assay meanwhile we are able to detect neurofilament light protein not only in CSF but also in plasma in very low concentrations [10]. Today there is a broad agreement stemming from research in neurological disorders and neurodegenerative diseases that plasma levels of neurofilament light protein reflect those in the cerebrospinal fluid and reliably reflect the degree of axonal damage in the brain [7,25,26].

Neurofilament light protein in affective disorders

In comparison to neurological and neurodegenerative diseases there is a relative paucity on data regarding involvement of neurofilament light protein in affective disorders. In a cross-sectional study of 78 elderly women (mean age 73.9 ± 3.2 years) without dementia within 10 years after having undergone a lumbar puncture in 1992 11 women were diagnosed with major depression at this time. Those with major depression had higher levels of neurofilament light protein in cerebrospinal fluid compared to participants without depression [27]. In a recent study assessing a large group of euthymic bipolar disorder patients (n = 133) elevated levels of neurofilament light protein were found in cerebrospinal fluid compared to healthy controls [28]. Furthermore, there was a positive association between elevated concentrations of neurofilament light protein and ongoing treatment with atypical antipsychotics [28]. However, in a prospective study of bipolar disorder patients no clear relationship between baseline concentrations of neurofilament light protein in cerebrospinal fluid and poor clinical outcomes in a 6–7-year follow-up could be demonstrated [29]. On the surface, these results seem to speak against an involvement of ongoing axonal damage in severe clinical outcomes in affective disorders. It is important to mention that assessments in these studies were made at baseline when patients were in an euthymic state, meaning that they are not classifiable as treatment resistant. Poor clinical outcomes are not necessarily reflecting treatment resistance and therefore speak not against our line of thought that treatment resistance in major depression is associated with persistent axonal damage.

Evaluation of the hypothesis

In order to evaluate our hypothesis that treatment resistant major depression is associated with persistent axonal damage we aim to measure concentrations of neurofilament light protein in plasma of a patient population suffering from severe chronic and treatment resistant major depression. We currently have the unique chance to study a group of 50 treatment resistant severe depressed patients with defined symptomatic homogeneity. These patients will be studied with regards to putative antidepressant efficacy of treatment with deep brain stimulation of the superolateral branch of the medial forebrain bundle (slMFB).

Despite the symptomatic homogeneity we take the possible neurobiological heterogeneity of major depression into account by including variables about the type of depression (melancholic, atypical), possible comorbid personality disorders as well as early and current life stress events.

Consequences of the hypothesis and discussion

There is an abundance of data pointing to structural volume loss correlated to time spent in untreated depression. This can plausibly be explained by persistent or past axonal damage. Indeed, persistent axonal damage could reflect the chronic process and failure to respond to established antidepressant therapies independently of being a cause or a consequence of treatment resistance.

In disorders like Multiple Sclerosis or Alzheimer's Disease the involvement of axonal damage is more established by radiological or cerebrospinal fluid abnormalities and clinical symptoms; this is not the

case in affective disorders, since their diagnoses are still based on clinical criteria only. One reason could be that the neuropathological processes in these disorders are too subtle to be assessed with today's methods. In conclusion there is still a significant need for sensitive techniques detecting and reflecting well defined neuropathological mechanisms in affective disorders.

With respect to the aforementioned measuring neurofilament light protein in plasma of patients with treatment resistant major depression could not only shed more light on its neuropathological mechanisms but help establishing such objective and neurobiological criteria in affective disorders also. Using single-molecule enzyme-linked immunosorbent assays a diagnostic procedure allowing lower invasiveness is accessible for severely depressed patients. Due to strong evidence that plasma concentrations reflect those in CSF invasive lumbar punctures could be avoided. Even if increased neurofilament light protein levels cannot count as a depression specific biomarker the strong correlation between CSF and plasma concentrations makes them superior to other biomarkers like proinflammatory cytokines. Establishing the characteristics of a sensitive and low invasive biomarker neurofilament light protein could be not only a promising biomarker for diagnostic purpose in treatment resistant major depression but also in purpose of monitoring disease process and treatment response.

Conflicts of interest

None of the authors state any conflict of interest regarding this manuscript.

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