Review

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Review

Mental Disorders in Multiple Endocrine Neoplasia Type 1

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Abstract

Menin, the product of Multiple Endocrine Neoplasia type 1 (*MEN1*) gene, is a scaffold protein, the lack of which generates the development of a tumor syndrome primarily affecting the endocrine organs. Although it is classified as an oncosuppressor, menin is a ubiquitous protein whose expression is also abundant in non- endocrine tissues such as the central nervous system, where knowledge of menin's role still remains limited. In this article, we have tried to draw attention to an underestimated clinical aspect of MEN1 syndrome, i.e., the psychological/psychiatric manifestations, in which menin deficiency could have an important function. Our aim is to highlight that a multidisciplinary team caring for a MEN1 patient throughout his or her life should include professionals such as psychologists and psychiatrists, in order to better manage any mental illness associated with the syndrome and to further improve the patient's quality of life.

Keywords: MEN1; mental disorders; tumors; behavior; hormones; psychologists; psychiatrists

1. Introduction

The relationship between mental and endocrine disorders is complex and very often bidirectional [1]. Multiple endocrine neoplasia type 1 (MEN1) is a rare hereditary cancer syndrome caused by germline heterozygous loss-of-function mutations in the *MEN1* gene, which result in the absence or abnormal production of the oncosuppressor protein menin and is causal of MEN1 tumors genesis [2]. The classic MEN1 clinical picture is represented by the occurrence of adenomas in the endocrine organs of the so-called 'P-triad' (i.e., parathyroid, endocrine pancreas and pituitary). However, around 20 different tumors have been described to be associated with the syndrome [3].

Usually, clinicians suspect a MEN1 case when a patient presents at least two of the three main endocrine tumors, or one of these tumors in presence of a family history of the disease [3]. To confirm the MEN1 diagnosis, the genetic MEN1 mutation is the diagnostic test that allows the search in the proband's relatives [2].

Although the life expectancy of MEN1 patients is believed to be reduced compared to general population, due to the rate of recurrence and aggressiveness of the tumors, the prognosis becomes more favourable if an earlier diagnosis is made and when the patient is taken care by a multidisciplinary medical team, specialized in the treatment of the disease-related disorders [2].

The *MEN1* gene has been found very well conserved across the evolution and the orthologs of its product, menin protein, can be detected in several organisms of the animal kingdom [4,5]. Menin is a ubiquitously expressed scaffold protein whose function appears to be tissue-specific [6]. Main known menin functions are related to its oncosuppressor role, while, even if menin is abundantly expressed in different tissues including the central nervous system (CNS), its role in non-endocrine

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organs is still poorly understood. Interestingly, homozygous deletion of the *MEN1* gene is genetic major structural defects of the embryonal neural tube closure lethal, far [6]. Furthermore, the age-dependent *MEN1* gene expression in the hippocampal and cortical regions of the CNS supports the possible involvement of menin in the formation and plasticity of neuronal synapses, as well as in cognition, learning and memory processes [7–9].

This manuscript focuses into the complex relationship between some endocrine disorders associated with MEN1 syndrome (i.e., hyperparathyroidism, hyperprolactinemia, and hypoglycemia) and mental illnesses, trying also to gain new insights into a possible direct involvement of menin in the development of psychiatric disturbances.

2. Methods

We performed an extensive search of PubMed, a bibliographic database, for papers demonstrating a correlation between endocrine and mental diseases and papers focusing on the possible involvement of menin in the onset of psychological and psychiatric disorders. Studies published between 1953 and 2025 have been examined. MEN1, menin, CNS, mental disorders, endocrinopathies, psychiatry diseases and endocrine tumors have been used as key words for the research.

3. MEN1-Related Tumors and Mental Disorders

Not always at the arrival at the hospital of an individual with behavioral disorders or neurological problems physicians assess the underlying the endocrine disorders, adopting a reductive approach, focused solely on mere symptomatic treatment. Although behavioral changes are rarely pathognomonic of a given disease, recognition of these concomitant endocrine disturbances would make possible an appropriate pharmacological treatment with potential advantages for the behavioral symptomatology [1]. Few examples will follow.

Insulinoma is a rare pancreatic beta-cell tumor that occurs in 1-4 people per million per year [10]. Despite this, it remains a common functioning pancreatic cancer in MEN1 patients, accounting for 10-30% of all pancreatic neuroendocrine tumors [11].

The clinical consequences of insulinoma are a rapid drop in blood glucose levels (hypoglycaemia) that can lead to weakness, confusion, dizziness, seizures and even coma and death [12–14]. Because insulinoma patients often manifest neurological and psychiatric disorders, misdiagnosis can lead not only to the wrong treatment with psychotropic or anticonvulsant drugs, but also to a delay in the diagnosis of the tumor, which today is estimated to be as long as two years from the onset of symptoms [15]. This can result in cognitive impairment in children due to recurrent episodes of hypoglycaemia [16,17], as well as the possibility of developing metastases, which are more frequent in MEN1 patients [11]. Medical therapy is usually based on the use of diazoxide, somatostatin analogues or frequent small meals to avoid prolonged fasting. However, in the event of pharmacological failure, surgery is often used, which may involve enucleation of the tumour or distal or partial pancreatectomy [3,17].

Although it is rare for hypoglycemia, due to an insulinoma, to be the first symptom leading to the diagnosis of MEN1, three cases have been reported in the literature where this has occurred [18–20]. Specifically, as all three young patients initially presented with neurological/psychiatric pathologies ranging from seizures, confusion to altered mental status and manic-depressive behavior, so the initial pharmacological therapy was aiming to treat the neuropsychiatric symptoms [18–20]. It was only the subsequent blood glucose monitoring that led clinicians to discover the presence of an insulinoma and only thereafter to suspect and diagnose MEN1 syndrome [18–20].

The interesting aspect is that although the correct blood glucose level were reestablished, one patient showed no improvement on the psychiatric symptomatology, leading to speculate that mutations in the *MEN1* gene may predispose to the development of mental disorders [20].

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Among the endocrine disorders that characterize the MEN1 phenotype, primary hyperparathyroidism (PHPT) occurs in almost the entire MEN1 population with a multi-glandular involvment [3]. This condition results in constantly elevated serum levels of parathyroid hormone (PTH), leading, if untreated, to hypercalcemia, with consequent development of kidney stones, osteoporosis, abdominal cramps, fatigue, as well as cardiac problems [21,22]. However, it is necessary to consider that PTH1R is also expressed in different areas of the CNS, as well as PTH itself and its related peptides (PTHrP), including tuberoinfundibular peptide of 39 (TIP39 or PTH2) [23]. Indeed, the PTH/PTHrP/PTH1R system appears to be involved in mechanisms of neurodegeneration and neuroinflammation, which underlie the development of both neurological and psychiatric diseases [23]. In the CNS, in addition to PTH1R, also the expression of PTH type2 receptor (PTH2R) has been found, which is able to bind mainly TIP39 and consequently influence cognitive processes, such as responses to stress and emotions [24]. In relation to this, several neuropsychiatric disorders are often associated with PHPT condition, including depression [25], which would appear the most common mental disease associated with the high blood levels of PTH, followed by anxiety, irritability, apathy, and fatigue [26–29]. Unfortunately, studies evaluating whether there was an improvement in neuropsychiatric symptoms after parathyroidectomy have shown conflicting data [30]. Neverthless, some surgical organizations, such as the American Association of Endocrine Surgeons, recommend that patients with PHPT should be routinely evaluated for the possible occurrence of neurological and/or psychiatric manifestations, and if they are attributed to the PHPT condition, the performance of parathyroid surgery is strongly suggested [26].

Finally, the pituitary tumor completes the classic clinical picture of the MEN1 patient and include most frequently prolactinoma with an increase of circulating prolactin (PRL), leading the sufferer to experience symptoms, such as amenorrhea, galactorrhea, impotence, headache and libido decrease [3,31]. PRL is a polypeptide hormone with a length of 199 amino acids and molecular weight of 23 kDa, which is mainly produced and secreted by adenohypophysis cells [32]. Although this hormone has the main function of inducing lactation in women, it is interesting how since the 1980s PRL has been presented as a “stress hormone”, as in different stress conditions PRL production increases [33,34]. Despite this, it is reported that patients with prolactinoma often display hostile, anxious, irritable, depressive behaviours and sleep disturbances [35–37], which could be due to the increasing frustration of not accepting the hardy changes [38]. However, such altered mental states could also be referred to hyperprolactinemia itself and the consequent alteration of the tuberoinfundibular neuron function, dopamine production and increased secretion of hypothalamic vasoinhibins, arise development of anxiety and depression [39,40].

To date, treatment of prolactinoma include pharmacological dopaminergic (cabergoline and bromocriptine), surgical, and/or radiotherapic approaches [41]. Treatment with dopaminergic drugs, especially at high doses can lead to the development of psychiatric disorders, such as impulse control disorders, psychosis, manic episodes and hallucinations, which tend to resolve with discontinuation of treatment [32]. The relationship between PRL levels and anxiety/depressive manifestations is still not entirely clear. This is probably due to the fact that, when the endocrinologist tend to focus exclusively to treat endocrine symptoms, often ignoring neurological and psychiatric complications. In light of all the above, the psychiatrists when dicharge for managing a mental illness should consider underlying endocrine disorders, including MEN1. Conversely, the endocrinologists managing an endocrine disease or syndrome should also value the potential neuropsychiatric complications. This is certainly true for MEN1.

4. Role of Menin in the Physiopathology of the Nervous Central System

The fact that orthologues of menin have been found in organisms belonging to different animal kingdoms seems to suggest that biological roles of the protein are fundamental from an evolutionary point of view for different animal species, including humans. However, studies about functions of this scaffold protein have mainly focused on its role in the development of MEN1-associated tumors, taking less account of other possible cellular mechanisms in which menin may be involved.

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The expression of the *MEN1* gene varies during embryogenesis, bringing to light that its expression was high from the early stages of embryogenesis throughout the entire body and restricted to certain tissues as gestation progressed [42,43]. Also, several tissues taken from a 20-week-old human foetus (i.e., pituitary, brain, thymus, testis, kidney, thyroid, adrenal and heart) expressed menin, which was not found in the liver, pancreas, lung, and skin, leading the scientists to hypothesize that the oncosuppressor protein is probably differentially expressed in various times during embryogenesis and in adulthood [44]. However, although high *MEN1* gene expression was observed at the human CNS level, limited attention has been given to the potential role of menin in neuronal pathophysiology.

In 2001, the first research on the potential effect of menin in CNS was shown in the mollusc Lymnaea, where the oncosuppressor protein appears to be a pivotal factor in synapses formation in central neurons [9].

In addition, it seems that the total lack of menin expression in mouse embryos resulted in premature death of the organism due to defects in neural tube closure, as well as the development of an abnormal cephalic structure with opening and protrusion of the midbrain and forebrain [6].

Only in the last years, the scientific community focused its attention on the possible menin role in the CNS, discovering that both in Lymnaea and mice, menin is able to influence neuronal synapse formation and plasticity, regulating not only the transcription of the alpha5 subunit of nicotinic receptors, but also the normal clustering of their alpha7 subunits [45], linked to schizophrenia and epilepsy [46,47].

Furthermore, the hypothesis that menin contributes to the proper development and functioning of the CNS is reinforced by the fact that this protein is capable of increasing transcription of the p35 factor, maintaining Cdk5 activity, and positively influencing neuronal development in the hippocampus region [7,48]. Additionally, Batool et al. [48], also confirmed that in the early stages of murine embryogenesis menin is generally expressed throughout the body, while during fetal growth the protein's expression is restricted to brain's centres that are responsible for controlling learning, memory and cognition processes [48]. Beyond that, in hippocampal neurons, menin showed a high degree of colocalization with the presynaptic protein Synaptogamin [1] and the postsynaptic protein PSD-95, suggesting an its possible role in the processes of synapse formation and plasticity that underlie memory and learning [48].

Based on all that has been reported, we can conclude that it is not possible to restrict the functionality of menin to the only oncosuppressor action, but it would be worthwhile to further investigate its possible roles in tissues that are not considered affected by *MEN1* gene mutations, including the CNS. This could lead to a better understanding of whether mutations of the *MEN1* gene may underlie the onset also of neurological and psychiatric disorders, such as depression. Major depression disorder (MDD) is defined as a psychiatric disease that afflicts millions of people worldwide, represent one of the major causes of disability [49,50], and is characterized by a complete loss of interest in life, a mood of discouragement and a marked tendency to suicidal thoughts [51]. Although the mechanisms predisposing to an increased risk of developing MDD are still not entirely clear, in recent years, numerous studies have reported that astrocyte dysfunction may underlie the pathogenesis of MDD [52–54].

If one were to ask what kind of relationship might exist between MDD and an oncological disorder such as MEN1, the answer lies in some recent scientific evidence showing reduced MEN1 gene expression in mouse astrocytes exposed to chronic unpredictable mild stress (CUMS) or lipopolysaccharide [55]. In fact, the *MEN1* deficiency in these cells leads to increased activity of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) transcription factor and augmented production of the pro-inflammatory cytokine IL-1β, resulting in depressive-like behaviour in the animals, which improved only with IL-1β receptor antagonist or NF-κB inhibitor administration [55].

Most importantly, it would appear that a specific single nucleotide polymorphism (SNP) of the *MEN1* gene (i.e., rs375804228) correlates with an elevated risk of developing MDD, given that this

 doi:10.20944/preprints202601.2290.v1

polymorphism causes the substitution of the amino acid glycine with aspartic acid at position 503 (G503D), thus preventing the interaction of menin with the p65 protein and consequently activating the NF-κB/IL-1β signalling pathway [55].

The hypothesis that menin is an important protein for the proper functioning of astrocytic cells is supported by the fact that the use of Astilbine is able to alleviate the depressive behavior of specific mouse models by increasing precisely the expression of menin in astrocytes, inhibiting the production of Nf-kB and thus reducing the inflammatory state of the astrocytic cells [56]. Moreover, loss of menin causes the parvalbumin (PV) neurons dysfunction, the disruption of which is closely linked to the onset of depression. In particular, the absence of the protein in PV interneurons leads not only to an increased expression of parvalbumin with depressive-like behaviour in the animals, but also a reduced antidepressant effects of ketamine [57].

While the biological link between MEN1 and MDD has been explored, very little is known about the role of menin in the pathogenesis of other mental illnesses. An example is offered by the fact that the over- expression or lack of menin could underlie the onset of autism-like behaviour in mice [58]. Specifically, the oncosuppressor protein is capable of interacting with the Alpha Thalassemia/Mental Retardation Syndrome X-Linked (Atrx) factor in excitatory neurons and, through histone methylation, regulating the transcription of the FOXG1 (Forkhead box G1) gene, whose mutations underlie the development of encephalopathies and autism disorders [58].

Therefore, menin could be an important player in the development of some psychiatric illness, and in particular of MDD. However, the latter is a complex disease that probably cannot be caused by the alteration of a single gene, but rather from a combination of several genetic, epigenetic and environmental factors [59]. Despite this, serious consideration should be given to learning more about the relationship between menin deficiency and the development of MDD, in order to better understand whether this protein may be a marker for the onset of this pathology, as well as to assess whether MEN1 patients could have a higher risk of incurring in the psychiatric disorder.

5. Considerations

It is now well known that there is a complex bidirectional relationship between endocrine disorders and psychiatric/neurological diseases, although the underlying biological mechanisms are not yet fully understood. Over the years, scientific evidences have suggested that inflammatory processes in the CNS play an important role in the development of psychiatric conditions such as depression, anxiety, and behavioral disorders [60]. Astrocytes, the most abundant glial cells, have attracted a great deal of attention in recent years because, among their many functions, they are able to protect the CNS from the entry of pro- inflammatory cytokines and suppress neuroinflammatory processes. Moreover, morphological abnormalities of these cells have been observed in the brains of individuals who died by suicide [60]. As previously reported, MEN1 gene deficiency at the astrocyte level could be associated with the onset of depression [55].

MEN1 syndrome is an inherited endocrine disorder caused by loss-of-function mutations in the MEN1 gene, resulting in the inability to produce menin protein and the subsequent growth of multiple, generally benign tumors in both endocrine and non-endocrine tissues [2].

Although the function of menin as an oncosuppressor is fairly well understood, its role in the CNS remains to be elucidated. Nonetheless, mice subjected to a stress load showed reduced menin expression in two of the brain areas most implicated in depression symptomatology [55]. Moreover, the hypothesis that menin may play a role in the development of psychiatric disorders is also supported by MEN1 patients themselves, who often report a low quality of life and suffer from anxiety and depression [61]. These preliminary data support the raising of two questions: Could the CUMS be associated with the constant anxiety of the MEN1 patient? How much could the lack of menin affect the likelihood of the risk to develop mental disorders?

A clinical case that aroused our curiosity is that where a 59-year-old woman who was hospitalized and treated pharmacologically for psychotic episodes was later diagnosed as a MEN1 patient. Although someone might have thought that the hallucinations, catatonia, and delusions

 doi:10.20944/preprints202601.2290.v1

might have been due to the clinical tumor picture, she showed no improvement in her psychiatric symptoms after undergoing parathyroidectomy and pancreasectomy, which tragically led her to an act of suicide [62]. The interesting aspect described in this brief report is that the patient in question did not exhibit the classic psychiatric manifestations of schizophrenia, leading clinicians to conclude that delusions, hallucinations, and catatonia could thus represent some of the psychiatric disorders that could be directly related to MEN1 syndrome.

In addition, two acts of suicide among MEN1 patients have been reported in the literature, but it is likely that there are more that have not yet been described. Although two cases do not represent a high number, one must consider this number within a "rare population". Therefore, clinicians should broaden their approach to MEN1 patients, not limiting the management to biochemical and instrumental tests, but including also a mental health assessment.

6. Conclusions

The protein menin itself may play an important role in the development of psychiatric disorders, especially those related to neuroinflammatory processes, such as MDD. However, the molecular pathways involving menin at the CNS level remain largely unknown, and a better understanding would be needed to further investigate the possible relationship between MEN1 syndrome and mental illness.

It should be reiterated that, although rare, psychiatric symptoms could mask more complex diseases, such as MEN1, which, if diagnosed early, ensuring the best treatment to the patients.

On the other hand, if a MEN1 diagnosis has already been made, one should consider that this may cause anxiety, depression, and stress due to the chronic nature of the disease and its potential complications. In addition, the awareness of having to deal with regular check-ups, surgery and the possibility of developing multiple tumors can significantly affect the patient's quality of life. In conclusion, it is recommended that the multidisciplinary team that follows the MEN1 patient over time includes also psychologists and psychiatrists, to better manage the mental aspects, which are often underestimated and can have devastating consequences in the lives of these patients.

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