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Review

Mental Disorders in Patients with Multiple Endocrine Neoplasia Type 1

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Abstract

Menin, the product of the Multiple Endocrine Neoplasia type 1 (*MEN1*) gene, is a scaffold protein, the lack of which leads to the development of a tumor syndrome primarily affecting 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 aim 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 patients with *MEN1* throughout their lives 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* gene; menin; mental disorders; psychiatrists; psychologists; depression

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 (with a prevalence of 1 in 30,000 individuals), caused by germline heterozygous loss-of-function mutations in the *MEN1* gene. This results in the absence or abnormal production of the oncosuppressor protein menin, which is the cause of tumors' onset [2]. The classic clinical presentation of *MEN1* 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]. Furthermore, age-related penetrance has been observed for the syndrome, reaching over 50% by the second decade of life and approximately 95% by the age of 40 years [3].

Usually, clinicians suspect a *MEN1* case when a patient presents at least two of the three main endocrine tumors or with one of these tumors in the presence of a family history of the disease [3]. To confirm a *MEN1* diagnosis, a genetic test needs to be performed to detect possible *MEN1* gene mutations, allowing the screening of the proband's relatives [2].

Due to the high recurrence rate and aggressiveness of the tumors, life expectancy in patients with *MEN1* is believed to be reduced compared to the general population. However, prognosis becomes more favourable if the diagnosis is made as early as possible

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and when the patient is managed by a multidisciplinary medical team specialized in the treatment of the disease-related disorders [2].

The *MEN1* gene has been found to be very well conserved across the evolution of animal species, and the orthologs of its product, the menin protein, have been detected in several organisms across the animal kingdom [4,5].

Even though menin's function appears to be tissue-specific6, mostly due to its onco-suppressor role, this scaffold protein is actually ubiquitously expressed. It can be found in many different tissues, including the central nervous system (CNS). Although its role in non-endocrine organs is still poorly understood, some studies suggest that menin is an important protein for the development and proper functioning of the CNS. In fact, deletion of the *MEN1* gene in the embryo cause significant structural defects during neural tube closure, resulting in the death of the organism [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 on the complex relationship between some endocrine disorders associated with *MEN1* syndrome (i.e., hyperparathyroidism, hyperprolactinemia and hypoglycemia) and mental illnesses. It also aims to provide new insights into the 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 were examined. *MEN1*, menin, CNS, mental disorders, endocrinopathies, psychiatry diseases and endocrine tumors were used as key words for the research.

3. *MEN1*-Related Tumors and Mental Disorders

Upon arriving at the hospital, patients with behavioral disorders or neurological issues are often poorly assessed: physicians may overlook possible underlying endocrine disorders, adopting a reductive approach and focusing merely on symptomatic treatment.

This is also because there is no real communication between specialists, who tend to focus almost exclusively on managing the symptoms associated with the condition they are specialized in, possibly resulting in early warning signs being overlooked. However, despite behavioral changes being rarely pathognomonic for a specific disease, recognition of these concomitant endocrine disturbances can enable appropriate pharmacological treatment with potential advantages for the behavioral symptomatology [1]. A few examples are discussed below.

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 patients with *MEN1*, accounting for 10–30% of all pancreatic neuroendocrine tumors [11].

The clinical consequences of insulinoma are rapid drops in blood glucose levels (hypoglycaemia), which 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 patients

with *MEN1* [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 tumor enucleation or distal or partial pancreatectomy [3,17].

Even though hypoglycemia caused by an insulinoma is rarely the first symptom leading to the diagnosis of *MEN1*, three cases have been reported in the literature where this has occurred [18–20]. More specifically, all three young patients initially presented with neurological/psychiatric pathologies ranging from seizures, confusion to altered mental status and manic-depressive behavior. Initial pharmacological therapy aimed to treat the neuropsychiatric symptoms [18–20], but 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].

Interestingly, despite the correct blood glucose levels being reestablished in all patients, one of them showed no improvement in the psychiatric symptomatology. This led to the speculation that mutations in the *MEN1* gene could make an individual more susceptible to the development of mental disorders [20].

Among the endocrine disorders that characterize the *MEN1* phenotype, primary hyperparathyroidism (PHPT) occurs in almost the entire population with *MEN1* and typically involves multiple glands3. 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 are 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, the expression of PTH type 2 receptor (PTH2R) has also 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 the PHPT condition, including depression [25], which would appear as 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 is an improvement in neuropsychiatric symptoms after parathyroidectomy have shown conflicting data [30]. Nevertheless, 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 advised [26].

Finally, pituitary tumors complete the classic clinical picture of patients with *MEN1*. These most frequently include prolactinomas with an increase in circulating prolactin (PRL) levels, leading symptoms such as amenorrhea, galactorrhea, impotence, headache and libido decrease [30,31]. PRL is a polypeptide hormone with a length of 199 amino acids and a molecular weight of 23 kDa, which is mainly produced and secreted by adenohypophysis cells [32]. Even though this hormone has the main function of inducing lactation in women, PRL has been presented as a "stress hormone" since the 1980s, as PRL production increases under different stress conditions [33,34]. Despite this, it is reported that patients with prolactinoma often display hostile, anxious, irritable or depressive behaviors and sleep disturbances [35–37], which could be due to the increasing frustration of not accepting the huge impact this disease has on their life [38]. However, such altered mental states, including anxiety and depression, may also be referred to hyperprolactinemia itself and

the consequent alterations in tuberoinfundibular neuron function, dopamine production and increased secretion of hypothalamic vasoinhibins [39,40].

To date, treatment for prolactinoma includes pharmacological dopaminergic (cabergoline and bromocriptine), surgical, and/or radiotherapeutic 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 upon 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 endocrinologists tend to focus exclusively on treating endocrine symptoms, often ignoring neurological and psychiatric complications.

In light of all the above, the psychiatrists who manage mental illnesses should consider underlying endocrine disorders, including *MEN1*. On the other hand, endocrinologists treating an endocrine disease or syndrome should remain attentive to potential neuropsychiatric complications.

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

The presence of orthologues of menin in organisms across different animal kingdoms suggests that the biological roles of the protein are fundamental from an evolutionary point of view for different animal species, including humans. However, studies on the functions of this scaffold protein have mainly focused on its role in the development of *MEN1*-associated tumors, with less attention given to other possible cellular mechanisms in which menin may be involved.

Studies have shown that the expression of the *MEN1* gene varies during embryogenesis in mice: in the early stages, it is high throughout the entire body, and it becomes restricted to certain tissues as gestation progresses [42,43]. This has been proven in humans as well, when 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 [44]. This have led scientists to hypothesize that the oncosuppressor protein is probably differentially expressed at various stages of embryogenesis and in adulthood in humans [44].

Considering these fundings and the high *MEN1* gene expression observed in 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 the CNS was conducted in the mollusc Lymnaea, where the oncosuppressor protein appeared to be a pivotal factor in synapse formation in central neurons [9].

In addition, it seems that the total lack of *MEN1* expression in mouse embryos resulted in premature death of organisms, predominantly between E11.5 and E13.5 stages. This lethality is likely due to various anomalies in organ growth and development. In particular, defects in neural tube closure, as well as the development of an abnormal cephalic structure with opening and protrusion of the midbrain and forebrain, were observed at E11.5–12.5 stages. Additionally, cardiac and hepatic defects were found in these *Men1*-null embryos during the same stages of embryogenesis [6].

Only in the last years, the scientific community focused its attention on the possible role of menin in the CNS, discovering that both in Lymnaea and mice, the protein is able to influence neuronal synapse formation and plasticity by regulating not only the transcription of the α5 nAChR subunit but also the normal clustering of their *α7* nAChR subunits [45], which have been 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 increas-

ing transcription of the p35 factor, maintaining Cdk5 activity, and positively influencing neuronal development in the hippocampus region [7,48]. Additionally, Batool et al. [48] confirmed that during the early stages of murine embryogenesis, menin is generally expressed throughout the body, while during fetal growth, the protein's expression is restricted to the brain's centers that are responsible for controlling learning, memory and cognition processes [48]. Beyond that, in hippocampal neurons, menin shows a high degree of colocalization with the presynaptic protein Synaptogamin1 and the postsynaptic protein PSD-95, suggesting its possible role in the processes of synapse formation and plasticity that underlie memory and learning [48].

Based on all data that has been reported, it is not possible to restrict the functionality of menin to only the oncosuppressor action, but it would be worthwhile to further investigate its potential 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 also contribute to the onset of neurological and psychiatric disorders, such as depression.

Major depressive disorder (MDD) is defined as a psychiatric disease that afflicts millions of people worldwide, representing one of the major causes of disability [49,50], and it is characterized by a complete loss of interest in life, a mood of discouragement and a marked tendency toward 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 play a key role in 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, *MEN1* deficiency in these cells leads to increased activity of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transcription factor and augmented production of the pro-inflammatory cytokine IL-1β. This results in depressive-like behavior in animals, which improved only by administration of IL-1β receptor antagonist or NF-κB inhibitor [55].

Most importantly, a specific single-nucleotide polymorphism (SNP) of the *MEN1* gene (i.e., rs375804228) appears to be correlated with an elevated risk of developing MDD, given that this 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 depressive behavior in specific mouse models. In particular, Astilbine increases menin expression in astrocytes and inhibits the production of NF-κB, reducing the inflammatory state of the astrocytic cells [56]. Moreover, loss of menin causes dysfunction in parvalbumin (PV) neurons, the disruption of which is closely linked to the onset of depression. Absence of the protein in PV interneurons not only leads to an increased expression of parvalbumin and depressive-like behavior in animals but also reduces the antidepressant effects of ketamine [57].

While the biological link between *MEN1* and MDD has already 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 may contribute to the onset of autism-like behavior 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, regulates

transcription of the FOXG1 (Forkhead box G1) gene, whose mutations are the main cause of the development of encephalopathies and autism disorders [58].

Therefore, menin could be an important player in the development of some psychiatric illnesses, particularly MDD. However, MDD is a complex condition that probably cannot be caused by alterations in 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 *MEN1* gene mutations and the development of MDD: specific mutations of the *MEN1* gene, causing significant changes in the structure, half-life or expression levels of the menin protein, could serve as potential "markers" for the onset of MDD. Moreover, a better understanding of the relationship between these mutations and MDD may help assess whether *MEN1* patients are at increased risk of developing this psychiatric disorder.

5. Considerations

Nowadays, it is well known that the existence of 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 evidence has 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]. Recently, astrocytes, the most abundant glial cells, have attracted a great deal of attention because, among their many functions, they are able to protect the CNS from the entry of pro-inflammatory cytokines and suppress neuroinflammatory processes [61]. Moreover, morphological abnormalities in 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 may 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 generally, the subsequent growth of multiple benign tumors in both endocrine and non-endocrine tissues [2].

Even though the function of menin as an oncosuppressor is well understood, its role in the CNS remains to be elucidated. Nonetheless, mice subjected to a stress load show 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 supported by observations in patients with *MEN1*, who often report low quality of life and experience anxiety and depression [62]. These preliminary data support the raising of two questions: could the CUMS be associated with the constant anxiety observed in patients with *MEN1*? How much could the lack of menin affect the likelihood of the risk to develop mental disorders?

Recently, a particular clinical case was reported in the literature: a 59-year-old woman, who was hospitalized and treated pharmacologically for psychotic episodes, was later diagnosed with *MEN1*. Although someone might have thought that the hallucinations, catatonia and delusions might have been due to the clinical tumor picture, she showed no improvement in her psychiatric symptoms after undergoing parathyroidectomy and pancreasectomy. Unfortunately, her psychiatric symptoms tragically led her to an act of suicide [63]. The interesting aspect described in this brief report is the exhibition of non-classic psychiatric manifestations of schizophrenia in the patient, leading clinicians to conclude that delusions, hallucinations and catatonia may thus represent some of the psychiatric disorders that could be directly related to *MEN1* syndrome.

In addition to this, another attempted suicide among patients with *MEN1* has been reported in the literature [20]: a young patient admitted with behavioral disorders was

later diagnosed with *MEN1* syndrome, showing the presence of pancreatic, pituitary and parathyroid tumors. Similarly to the case of the 59-year-old woman, no improvement in psychiatric symptoms was observed after tumor resection and pharmacological treatment to control hormone secretion. This suggests that such symptomatology could be linked to the pathology itself rather than to hormone dysregulation alone. Even if, at the moment, only these two cases are described in the literature, it is possible that there are others that were never reported. These two cases do not represent a high number, but this number must not be overlooked within a "rare population". Therefore, clinicians should broaden their approach in managing patients with *MEN1*, not limiting the management to biochemical and instrumental tests but also including mental health assessments.

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 is needed to further investigate the possible relationship between *MEN1* syndrome and mental illness.

It is of high importance to note that, although rare, psychiatric symptoms may mask more complex diseases, such as *MEN1*. If diagnosed early, the best treatment for these patients can be guaranteed.

Nevertheless, it is not always an obvious conclusion to assume that a patient is affected by *MEN1* based exclusively on psychiatric symptoms. This is further complicated by the variability of clinical presentation from patient to patient, even among individuals carrying the same mutation.

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, surgeries and the possibility of developing multiple tumors can significantly affect a patient's quality of life. In this regard, it has been observed that patients with *MEN1* experience a lower quality of life than the general population [64]. This finding is independent of biochemical control of the syndrome, suggesting that managing the condition based on blood test results alone does not constitute 'care of the patient' in the broader sense.

In conclusion, it is recommended that the multidisciplinary team managing patients with *MEN1* over time also include psychologists and psychiatrists to better address mental health aspects, which are often underestimated and can have devastating consequences in the lives of these patients.

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References

1. Reus, V.I. Behavioral Disturbances Associated with Endocrine Disorders. *Annu. Rev. Med.* **1986**, *37*, 205–214. [CrossRef] [PubMed]
2. Brandi, M.L.; Pieterman, C.R.C.; English, K.A.; Lines, K.E.; Shariq, O.A.; Marini, F.; Cuny, T.; Lewis, M.A.; Stratakis, C.A.; Perrier, N.D.; et al. Multiple Endocrine Neoplasia Type 1 (*MEN1*): Recommendations and Guidelines for Best Practice. *Lancet Diabetes Endocrinol.* **2025**, *13*, 699–721. [CrossRef]
3. Brandi, M.L.; Agarwal, S.K.; Perrier, N.D.; Lines, K.E.; Valk, G.D.; Thakker, R.V. Multiple Endocrine Neoplasia Type 1: Latest Insights. *Endocr. Rev.* **2021**, *42*, 133–170. [CrossRef]
4. Getz, A.M.; Visser, F.; Bell, E.M.; Xu, F.; Flynn, N.M.; Zaidi, W.; Syed, N.I. Two Proteolytic Fragments of Menin Coordinate the Nuclear Transcription and Postsynaptic Clustering of Neurotransmitter Receptors during Synaptogenesis between Lymnaea Neurons. *Sci. Rep.* **2016**, *6*, 31779. [CrossRef]
5. Chen, Y.-X.; Yan, J.; Keeshan, K.; Tubbs, A.T.; Wang, H.; Silva, A.; Brown, E.J.; Hess, J.L.; Pear, W.S.; Hua, X. The Tumor Suppressor Menin Regulates Hematopoiesis and Myeloid Transformation by Influencing Hox Gene Expression. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 1018–1023. [CrossRef]
6. Bertolino, P.; Radovanovic, I.; Casse, H.; Aguzzi, A.; Wang, Z.-Q.; Zhang, C.-X. Genetic Ablation of the Tumor Suppressor Menin Causes Lethality at Mid-Gestation with Defects in Multiple Organs. *Mech. Dev.* **2003**, *120*, 549–560. [CrossRef] [PubMed]
7. Zhuang, K.; Huang, C.; Leng, L.; Zheng, H.; Gao, Y.; Chen, G.; Ji, Z.; Sun, H.; Hu, Y.; Wu, D.; et al. Neuron-Specific Menin Deletion Leads to Synaptic Dysfunction and Cognitive Impairment by Modulating P35 Expression. *Cell Rep.* **2018**, *24*, 701–712. [CrossRef]
8. Xu, S.; Wu, H.; Wang, X.; Shen, X.; Guo, X.; Shen, R.; Wang, F. Tumor Suppressor Menin Mediates Peripheral Nerve Injury-Induced Neuropathic Pain through Potentiating Synaptic Plasticity. *Neuroscience* **2012**, *223*, 473–485. [CrossRef]
9. van Kesteren, R.E.; Syed, N.I.; Munno, D.W.; Bouwman, J.; Feng, Z.P.; Geraerts, W.P.; Smit, A.B. Synapse Formation between Central Neurons Requires Postsynaptic Expression of the *MEN1* Tumor Suppressor Gene. *J. Neurosci.* **2001**, *21*, RC161. [CrossRef] [PubMed]
10. Service, F.J.; McMahon, M.M.; O'Brien, P.C.; Ballard, D.J. Functioning Insulinoma—Incidence, Recurrence, and Long-Term Survival of Patients: A 60-Year Study. *Mayo Clin. Proc.* **1991**, *66*, 711–719. [CrossRef]
11. Thakker, R.V.; Newey, P.J.; Walls, G.V.; Bilezikian, J.; Dralle, H.; Ebeling, P.R.; Melmed, S.; Sakurai, A.; Tonelli, F.; Brandi, M.L.; et al. Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (*MEN1*). *J. Clin. Endocrinol. Metab.* **2012**, *97*, 2990–3011. [CrossRef]
12. Ding, Y.; Wang, S.; Liu, J.; Yang, Y.; Liu, Z.; Li, J.; Zhang, B.; Chen, Y.; Ding, M. Neuropsychiatric Profiles of Patients with Insulinomas. *Eur. Neurol.* **2010**, *63*, 48–51. [CrossRef]
13. Tesfaye, N.; Seaquist, E.R. Neuroendocrine Responses to Hypoglycemia. *Ann. N. Y. Acad. Sci.* **2010**, *1212*, 12–28. [CrossRef] [PubMed]
14. Correia, P.; Panchani, R.; Ranjan, R.; Agrawal, C. Insulinoma Presenting as Refractory Seizure Disorder. *F1000 Res.* **2012**, *1*, 15. [CrossRef]
15. Ozen, S.; Saz, E.U.; Celik, A.; Aydin, A.; Simsek, D.G.; Darcan, S. Many Admissions to the Emergency Departments with Recurrent Syncope Attacks and Seizures in an Adolescent Boy. *Eur. J. Pediatr.* **2009**, *168*, 761–763. [CrossRef]
16. Jaladyan, V.; Darbinyan, V. Insulinoma Misdiagnosed as Juvenile Myoclonic Epilepsy. *Eur. J. Pediatr.* **2007**, *166*, 485–487. [CrossRef]
17. Vezzosi, D.; Bennet, A.; Courbon, F.; Caron, P. Short- and Long-Term Somatostatin Analogue Treatment in Patients with Hypoglycaemia Related to Endogenous Hyperinsulinism. *Clin. Endocrinol.* **2008**, *68*, 904–911. [CrossRef]
18. de Paiva, A.R.B.; Castro, L.H.M.; Rodrigues, W.; Passarelli, V.; Jorge, C.L.; Brotto, M.W.I.; Hirata, M.T.A.; Marchiori, P.E. Multiple Endocrine Neoplasia Type 1 Presenting as Refractory Epilepsy and Polyneuropathy—A Case Report. *J. Neurol. Sci.* **2012**, *315*, 172–175. [CrossRef]
19. Winston, K.Y.; Dawrant, J. A Rare Case of Hypoglycaemia Due to Insulinoma in an Adolescent with Acutely Altered Mental Status. *J. Pediatr. Endocrinol. Metab.* **2014**, *27*, 773–776. [CrossRef] [PubMed]
20. Aoki, A.; Tsukada, T.; Yasuda, H.; Kayashima, S.; Nagase, T.; Ito, T.; Suzuki, T.; Matsukuma, S.; Kuwabara, N.; Yoshimoto, K.; et al. Multiple Endocrine Neoplasia Type 1 Presented with Manic-Depressive Disorder: A Case Report with an Identified *MEN1* Gene Mutation. *Jpn. J. Clin. Oncol.* **1997**, *27*, 419–422. [CrossRef] [PubMed]
21. Harrison, N.A.; Kopelman, M.D. Endocrine Diseases and Metabolic Disorders. In *Lishman's Organic Psychiatry*; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2009; pp. 617–688, ISBN 978-1-4443-1680-3.
22. Iwata, S.; Walker, M.D.; Di Tullio, M.R.; Hyodo, E.; Jin, Z.; Liu, R.; Sacco, R.L.; Homma, S.; Silverberg, S.J. Aortic Valve Calcification in Mild Primary Hyperparathyroidism. *J. Clin. Endocrinol. Metab.* **2012**, *97*, 132–137. [CrossRef]
23. Dettori, C.; Ronca, F.; Scalese, M.; Saponaro, F. Parathyroid Hormone (PTH)-Related Peptides Family: An Intriguing Role in the Central Nervous System. *J. Pers. Med.* **2023**, *13*, 714. [CrossRef]
24. Dobolyi, A.; Ueda, H.; Uchida, H.; Palkovits, M.; Usdin, T.B. Anatomical and Physiological Evidence for Involvement of Tuberoinfundibular Peptide of 39 Residues in Nociception. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 1651–1656. [CrossRef] [PubMed]

25. Espiritu, R.P.; Kearns, A.E.; Vickers, K.S.; Grant, C.; Ryu, E.; Wermers, R.A. Depression in Primary Hyperparathyroidism: Prevalence and Benefit of Surgery. *J. Clin. Endocrinol. Metab.* **2011**, *96*, E1737–E1745. [CrossRef] [PubMed]
26. Weber, T.; Keller, M.; Hense, I.; Pietsch, A.; Hinz, U.; Schilling, T.; Nawroth, P.; Klar, E.; Büchler, M.W. Effect of Parathyroidectomy on Quality of Life and Neuropsychological Symptoms in Primary Hyperparathyroidism. *World J. Surg.* **2007**, *31*, 1202–1209. [CrossRef] [PubMed]
27. Wilhelm, S.M.; Lee, J.; Prinz, R.A. Major Depression Due to Primary Hyperparathyroidism: A Frequent and Correctable Disorder. *Am. Surg.* **2004**, *70*, 175–179. [CrossRef]
28. Joborn, C.; Hetta, J.; Palmér, M.; Akerström, G.; Ljunghall, S. Psychiatric Symptomatology in Patients with Primary Hyperparathyroidism. *Upsala J. Med. Sci.* **1986**, *91*, 77–87. [CrossRef]
29. Lourida, I.; Thompson-Coon, J.; Dickens, C.M.; Soni, M.; Kuźma, E.; Kos, K.; Llewellyn, D.J. Parathyroid Hormone, Cognitive Function and Dementia: A Systematic Review. *PLoS ONE* **2015**, *10*, e0127574. [CrossRef]
30. Chandran, M.; Yeh, L.T.L.; de Jong, M.C.; Bilezikian, J.P.; Parameswaran, R. Cognitive Deficits in Primary Hyperparathyroidism—What We Know and What We Do Not Know: A Narrative Review. *Rev. Endocr. Metab. Disord.* **2022**, *23*, 1079–1087. [CrossRef]
31. Tritos, N.A.; Miller, K.K. Diagnosis and Management of Pituitary Adenomas: A Review. *JAMA* **2023**, *329*, 1386–1398. [CrossRef]
32. Rizzo, L.F.L.; Mana, D.L.; Serra, H.A.; Danilowicz, K. Hyperprolactinemia Associated with Psychiatric Disorders. *Medicina* **2020**, *80*, 670–680.
33. Reichlin, S. Prolactin and Growth Hormone Secretion in Stress. *Adv. Exp. Med. Biol.* **1988**, *245*, 353–376. [CrossRef] [PubMed]
34. Torner, L.; Toschi, N.; Pohlinger, A.; Landgraf, R.; Neumann, I.D. Anxiolytic and Anti-Stress Effects of Brain Prolactin: Improved Efficacy of Antisense Targeting of the Prolactin Receptor by Molecular Modeling. *J. Neurosci.* **2001**, *21*, 3207–3214. [CrossRef]
35. Fava, M.; Fava, G.A.; Kellner, R.; Buckman, M.T.; Lisansky, J.; Serafini, E.; DeBesi, L.; Mastrogiacomo, I. Psychosomatic Aspects of Hyperprolactinemia. *Psychother. Psychosom.* **1983**, *40*, 257–262. [CrossRef]
36. Johnson, M.D.; Woodburn, C.J.; Vance, M.L. Quality of Life in Patients with a Pituitary Adenoma. *Pituitary* **2003**, *6*, 81–87. [CrossRef]
37. Miao, X.; Fu, Z.; Luo, X.; Wang, J.; Yuan, L.; Zhao, S.; Feng, Y.; Huang, S.; Xiao, S. A Study on the Correlations of PRL Levels with Anxiety, Depression, Sleep, and Self-Efficacy in Patients with Prolactinoma. *Front. Endocrinol.* **2024**, *15*, 1369729. [CrossRef]
38. Pereira, H.S.; Naliato, E.C.; Moraes, A.B.; Gadelha, M.R.; Vieira Neto, L.; Almeida, R.M.; Nardi, A.E.; Violante, A.H. Body Self-Image Disturbances in Women with Prolactinoma. *Braz. J. Psychiatry* **2020**, *42*, 33–39. [CrossRef]
39. Mohankumar, P.S.; Mohankumar, S.M.; Quadri, S.K.; Voogt, J.L. Chronic Hyperprolactinemia and Changes in Dopamine Neurons. *Brain Res. Bull.* **1997**, *42*, 435–441. [CrossRef] [PubMed]
40. Zamorano, M.; Ledesma-Colunga, M.G.; Adán, N.; Vera-Massieu, C.; Lemini, M.; Méndez, I.; Moreno-Carranza, B.; Neumann, I.D.; Thebault, S.; Martínez de la Escalera, G.; et al. Prolactin-Derived Vasoinhibins Increase Anxiety- and Depression-Related Behaviors. *Psychoneuroendocrinology* **2014**, *44*, 123–132. [CrossRef]
41. Cozzi, R.; Ambrosio, M.R.; Attanasio, R.; Battista, C.; Bozzao, A.; Caputo, M.; Ciccarelli, E.; De Marinis, L.; De Menis, E.; Faustini Fustini, M.; et al. Italian Association of Clinical Endocrinologists (AME) and International Chapter of Clinical Endocrinology (ICCE). Position Statement for Clinical Practice: Prolactin-Secreting Tumors. *Eur. J. Endocrinol.* **2022**, *186*, P1–P33. [CrossRef] [PubMed]
42. Stewart, C.; Parente, F.; Piehl, F.; Farnebo, F.; Quincey, D.; Silins, G.; Bergman, L.; Carle, G.F.; Lemmens, I.; Grimmond, S.; et al. Characterization of the Mouse *MEN1* Gene and Its Expression during Development. *Oncogene* **1998**, *17*, 2485–2493. [CrossRef]
43. Guru, S.C.; Crabtree, J.S.; Brown, K.D.; Dunn, K.J.; Manickam, P.; Prasad, N.B.; Wangsa, D.; Burns, A.L.; Spiegel, A.M.; Marx, S.J.; et al. Isolation, Genomic Organization, and Expression Analysis of *MEN1*, the Murine Homolog of the *MEN1* Gene. *Mamm. Genome* **1999**, *10*, 592–596. [CrossRef]
44. Wautot, V.; Khodaei, S.; Frappart, L.; Buisson, N.; Baro, E.; Lenoir, G.M.; Calender, A.; Zhang, C.X.; Weber, G. Expression Analysis of Endogenous Menin, the Product of the Multiple Endocrine Neoplasia Type 1 Gene, in Cell Lines and Human Tissues. *Int. J. Cancer* **2000**, *85*, 877–881. [CrossRef]
45. Getz, A.M.; Xu, F.; Visser, F.; Persson, R.; Syed, N.I. Tumor Suppressor Menin Is Required for Subunit-Specific nAChR A5 Transcription and nAChR-Dependent Presynaptic Facilitation in Cultured Mouse Hippocampal Neurons. *Sci. Rep.* **2017**, *7*, 1768. [CrossRef] [PubMed]
46. Freedman, R.; Leonard, S.; Gault, J.M.; Hopkins, J.; Cloninger, C.R.; Kaufmann, C.A.; Tsuang, M.T.; Farone, S.V.; Malaspina, D.; Svrakic, D.M.; et al. Linkage Disequilibrium for Schizophrenia at the Chromosome 15q13-14 Locus of the Alpha7-Nicotinic Acetylcholine Receptor Subunit Gene (CHRNA7). *Am. J. Med. Genet.* **2001**, *105*, 20–22. [CrossRef] [PubMed]
47. Flomen, R.H.; Davies, A.F.; Di Forti, M.; La Cascia, C.; Mackie-Ogilvie, C.; Murray, R.; Makoff, A.J. The Copy Number Variant Involving Part of the Alpha7 Nicotinic Receptor Gene Contains a Polymorphic Inversion. *Eur. J. Hum. Genet.* **2008**, *16*, 1364–1371. [CrossRef]
48. Batool, S.; Zaidi, J.; Akhter, B.; Ulfat, A.K.; Visser, F.; Syed, N.I. Spatiotemporal Patterns of Menin Localization in Developing Murine Brain: Co-Expression with the Elements of Cholinergic Synaptic Machinery. *Cells* **2021**, *10*, 1215. [CrossRef]

49. CONVERGE consortium. Sparse Whole-Genome Sequencing Identifies Two Loci for Major Depressive Disorder. *Nature* **2015**, *523*, 588–591. [CrossRef] [PubMed]
50. Ferrari, A.J.; Charlson, F.J.; Norman, R.E.; Patten, S.B.; Freedman, G.; Murray, C.J.L.; Vos, T.; Whiteford, H.A. Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. *PLoS Med.* **2013**, *10*, e1001547. [CrossRef]
51. Canals, J.; Carbajo, G.; Fernández-Ballart, J. Discriminant Validity of the Eating Attitudes Test According to American Psychiatric Association and World Health Organization Criteria of Eating Disorders. *Psychol. Rep.* **2002**, *91*, 1052–1056. [CrossRef]
52. Rajkowska, G.; Stockmeier, C.A. Astrocyte Pathology in Major Depressive Disorder: Insights from Human Postmortem Brain Tissue. *Curr. Drug Targets* **2013**, *14*, 1225–1236. [CrossRef] [PubMed]
53. Sanacora, G.; Banasr, M. From Pathophysiology to Novel Antidepressant Drugs: Glial Contributions to the Pathology and Treatment of Mood Disorders. *Biol. Psychiatry* **2013**, *73*, 1172–1179. [CrossRef] [PubMed]
54. Wang, Q.; Jie, W.; Liu, J.-H.; Yang, J.-M.; Gao, T.-M. An Astroglial Basis of Major Depressive Disorder? An Overview. *Glia* **2017**, *65*, 1227–1250. [CrossRef]
55. Leng, L.; Zhuang, K.; Liu, Z.; Huang, C.; Gao, Y.; Chen, G.; Lin, H.; Hu, Y.; Wu, D.; Shi, M.; et al. Menin Deficiency Leads to Depressive-like Behaviors in Mice by Modulating Astrocyte-Mediated Neuroinflammation. *Neuron* **2018**, *100*, 551–563.e7. [CrossRef]
56. Yao, Y.; Man, L.; Du, J.; Wu, D.; Yang, L.; Peng, F.; Han, L.; Zhao, T.; Zhou, W. Astilbin Ameliorates Depressive-like Behavior Caused by Postnatal Immune Activation through Menin-Regulated Astrocyte Inflammation. *J. Affect. Disord.* **2022**, *301*, 87–98. [CrossRef] [PubMed]
57. Leng, L.; Zhuang, K.; Lin, H.; Ding, J.; Yang, S.; Yuan, Z.; Huang, C.; Chen, G.; Chen, Z.; Wang, M.; et al. Menin Reduces Parvalbumin Expression and Is Required for the Anti-Depressant Function of Ketamine. *Adv. Sci.* **2024**, *11*, e2305659. [CrossRef]
58. Zhuang, K.; Leng, L.; Su, X.; Wang, S.; Su, Y.; Chen, Y.; Yuan, Z.; Zi, L.; Li, J.; Xie, W.; et al. Menin Deficiency Induces Autism-Like Behaviors by Regulating Foxg1 Transcription and Participates in Foxg1-Related Encephalopathy. *Adv. Sci.* **2024**, *11*, e2307953. [CrossRef]
59. Bosker, F.J.; Hartman, C.A.; Nolte, I.M.; Prins, B.P.; Terpstra, P.; Posthuma, D.; van Veen, T.; Willemsen, G.; DeRijk, R.H.; de Geus, E.J.; et al. Poor Replication of Candidate Genes for Major Depressive Disorder Using Genome-Wide Association Data. *Mol. Psychiatry* **2011**, *16*, 516–532. [CrossRef]
60. Kaufmann, F.N.; Menard, C. Inflamed Astrocytes: A Path to Depression Led by Menin. *Neuron* **2018**, *100*, 511–513. [CrossRef]
61. Bhusal, A.; Afridi, R.; Lee, W.-H.; Suk, K. Bidirectional Communication Between Microglia and Astrocytes in Neuroinflammation. *Curr. Neuropharmacol.* **2023**, *21*, 2020–2029. [CrossRef]
62. Peipert, B.J.; Goswami, S.; Yount, S.E.; Sturgeon, C. Health-Related Quality of Life in *MEN1* Patients Compared with Other Chronic Conditions and the United States General Population. *Surgery* **2018**, *163*, 205–211. [CrossRef] [PubMed]
63. Kito, S.; Nakajima, T.; Yamadera, H.; Koga, Y.; Kosugi, S.; Hai, N. Multiple Endocrine Neoplasia Type 1 Presenting as Psychosis. *Am. J. Psychiatry* **2005**, *162*, 810–811. [CrossRef]
64. Berglund, G.; Lidén, A.; Hansson, M.G.; Oberg, K.; Sjöden, P.O.; Nordin, K. Quality of Life in Patients with Multiple Endocrine Neoplasia Type 1 (MEN 1). *Fam. Cancer* **2003**, *2*, 27–33. [CrossRef] [PubMed]