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The MEN1 Syndrome and the Impact on Patients and their Family

Bachelor Thesis Biomedical Sciences

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Abstract

In 2014, in the Netherlands, 350 to 400 people were suffering from the Multiple Endocrine Neoplasia Type 1 syndrome. These patients were most of the time surviving, but some ended up in malignancy and unfortunately into death (LUMC, 2014).

The Multiple Endocrine Neoplasia Type 1 Syndrome, also known as the MEN1 syndrome, is a rare inherited disease which affects several endocrine glands in the human body. As already stated, this disease is very uncommon since it occurs in 1 person in every 30,000 people (Norman, 2016). The MEN1 mutation passes down from generation to generation because each child of a MEN1 patient is having a 50% chance of inheriting the mutation which will eventually cause the disease (Falchetti et al., 2009).

When a person is a victim of the MEN1 syndrome, several endocrine glands are affected among which the parathyroid glands, pituitary gland, and pancreas, who can show an over-activity in the hormone production. This is also often correlated to the enlargement of those glands, resulting in an unequal growth. Thereby, some areas in the glands are growing rapidly, and become "lumpy", which are most of the time benign tumors, also known as adenomas (Norman, 2006).

The problem with Multiple Endocrine Neoplasia syndromes, is that it differs per person at which age the different endocrine glands will become over-active, so it depends when, and how someone should act. However, this overactivity and developing of adenomas is increasing in chance with age. Due to this case, it may occur that you already passed on the mutation because you were diagnosed on later age (Norman, 2006).

So, a lot of Multiple Endocrine Neoplasia Type 1 patients and their family are questioning themselves how they should handle with this syndrome when dealing with it. They are in doubt if a surgery is needed since there are complications with several treatments. Therefore, the question to be answered is: "What is the MEN-1a-Syndrome and how should these patients and their family deal with this disease?"

Several treatments can be done, which are different per affected endocrine gland. Patients can choose for the removal of the gland, tumor, or sometimes using medical treatment. When symptoms are mild, and the surgery is risky, doctors are discouraging treatments against the MEN1 syndrome to keep some quality of life. At the end, it is important to test regularly if your family members are having the MEN1 mutations, or when you are having overactivity in two or more MEN1-associated endocrine glands. This regularly testing is important to detect the disorder as soon as possible and intervene in the initial phase of the Multiple Endocrine Neoplasia Type 1 syndrome.

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1. The Problem with Multiple Endocrine Neoplasia Syndromes

Starting off with the reason why the Multiple Endocrine Neoplasia syndromes are seen as a problem. As early stated, the MEN 1 syndrome is normally an autosomal dominant inherited disease, but in some cases, it is sporadic. The most common tumors are parathyroid adenomas (90% of the cases), entero-pancreatic tumors (30%-70% of the cases), and pituitary adenomas (30%-40% of the cases). With the syndrome, it often occurs that several glands are affected at the same time, so the syndrome it is spread through the body. Thereby, the symptoms are arising at different ages, so you can also face the syndrome later in life. The diagnosis can be done clinically when a patient is presenting two or more Multiple endocrine Neoplasia type 1 tumors. The diagnosis can also be done familial when the patient has a MEN1-associated tumor, and it has a relative with MEN1 in the first degree. Lastly, a genetic diagnosis can be done when there are no obvious characteristics of the MEN1 syndrome. Since the symptoms of the MEN1 syndrome are widespread and diverse, it is hard to directly recognize the disease sometimes (Boro et al., 2020).

A 46-year-old woman experienced low blood glucose levels due to elevated insulin levels in the blood, which is called hyperinsulinemic hypoglycemia. It was diagnosed that the woman was suffering from several insulinomas, which are tumors in the pancreas. Thereby, in the history of her family, members had complaints with other endocrine glands, so after evaluations they found out she had primary hyperparathyroidism (PHPT) and prolactinomas. Those symptoms were suggesting that the woman carried the MEN1 syndrome, but the traditional hallmarks were not present. In this case report, they diagnosed the patient after doing clinical, familial, and genetic tests, and came to the discovery that huge kindred were affected with the MEN1 mutation. This case is emphasizing that it is important to search for the MEN1-associated tumors and screen family members genetically when there is clinically or biochemically suspicion (Boro et al., 2020).

Another case, a male in his early thirties, who went to the emergency department after suffering of abdominal pain, vomiting and nausea for weeks. When looking back at his history, they came to the discovery that he experienced in his late twenties already symptoms which referred to pituitary prolactinoma, which is later confirmed by MRI screening. The family history gave the insight that his paternal grandmother had pituitary tumors and his paternal aunt had a thymic tumor. When they found out there was clinical suspicion on MEN1 in the male, the endocrine system was checked to look at the hormone production in the body. After a lot of tests, the man turned out to have tumors in all the three endocrine glands associated with the MEN1 syndrome, and he was probably the carrier of the syndrome for years now (Keller et al., 2018).

Considering these case reports, it is seen that the symptoms are differing in every patient. The woman and the male find out they have the disease in different ways, with different experiments to diagnose them. It is hard to recognize the disease immediately, and people often look at the family history later in the stadium, so the chance that the MEN1 mutation is passed through generations already is big. In short, the problem with the MEN1 syndrome is that patients experience different symptoms at different ages, which makes it hard to diagnose them without doing a lot of tests and prevent the inheritance of the MEN1-mutation in time (Norman, 2016).

2. The MEN1 Syndrome

To answer the dilemma how patients and their family should deal with the MEN1 syndrome, it is important to go through the theory and mechanism of this disease. It is needed to look where the disease starts, how the genetics are influencing this, and which endocrine glands are affected by the MEN1-mutation. Thereby, of course a patient wants to know how the diagnosis procedure works, and what the prognosis is when living with the disorder, to have an idea how their future will look like.

2.1 MEN Type 1 and Type 2

As mentioned before, Multiple Endocrine Neoplasia syndromes are disorders that affect the endocrine system. These syndromes often form tumors in numerous endocrine glands, where they can start overactivity, which will eventually result in the overproduction of hormones. The MEN syndromes are inherited autosomal dominant and consists of four different types, from which the most common being types are MEN1 and MEN2 (Vellanki, 2014). The different MEN syndrome types and their corresponding symptoms are described in figure 1.

Firstly, MEN Type 1, which is also known as Multiple Endocrine Adenomatosis Type 1, and Wermer's Syndrome. With this syndrome, there is a germline-inactivating mutation of the MEN1 tumour-suppressor gene, which is normally encoding the protein menin (Norman, 2016). The disease usually involves tumors of the pancreas, pituitary gland, and parathyroid glands, where the overactive parathyroid glands are often the starting point of the disorder. When the parathyroid glands are showing an overactivity of the parathyroid hormone, it is called hyperparathyroidism, which will lead to high calcium levels in the blood (Vellanki, 2014).

Secondly, MEN Type 2 which consists of three different subtypes: Type 2A (90% of all the cases), Type 2B, and FMTC, a familial medullary thyroid carcinoma. Most patients with MEN2 are developing medullary thyroid carcinoma, which applies to all the three subtypes. The thyroid is managing the sending out of hormones to the rest of the human body, so the tumor over here causes the hormone balance to be out of balance. Thereby, some patients will develop a tumor in their adrenal gland, called pheochromocytoma, which is resulting in an extremely high blood pressure. The same as in the MEN1 syndrome, hyperparathyroidism can be developed, which results in high parathyroid hormone and calcium levels. Individuals with MEN2B, which is not a common case, can also develop tumors in nerve cells of the gastrointestinal tract, their lips, tongue, and eyelids, which occurs before the age of 10, also known as mucosal neuromass (Vellanki, 2014).

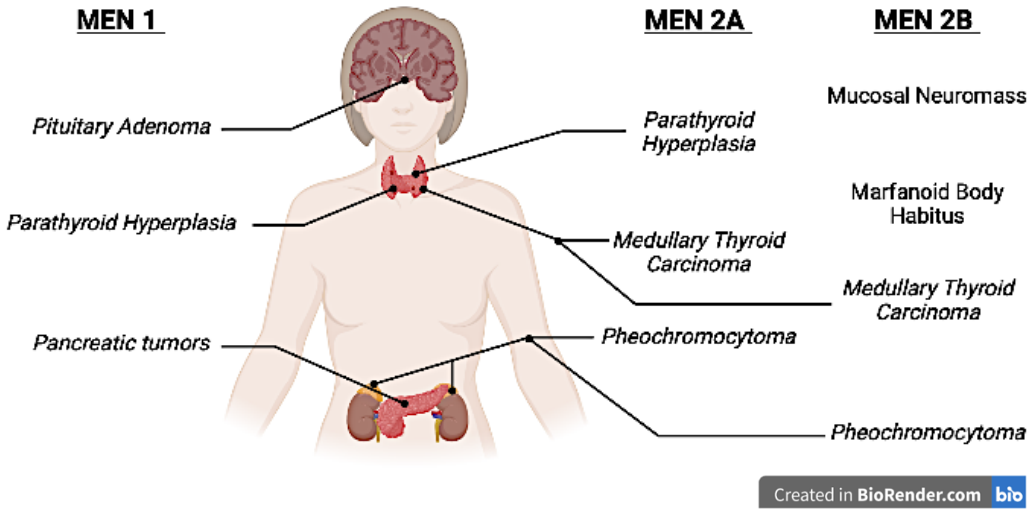

Figure 1: Multiple Endocrine Neoplasia Syndrome Types and Corresponding Symptoms

2.2 Menin

Then, the protein menin, which works as a tumor suppressor to prevent cells growing unchecked and too rapidly. When having mutations in this gene, which is the case with the MEN1 syndrome, tumours can grow easily (Agarwal et al., 1999).

In different studies, several mutations have been reported which disturb the protein interactions. However, less is known about the mechanisms how those mutations can lead to the inactivation of protein menin. Menin needs nuclear localization signals (NLSs), to bind the double-stranded DNA. When removing those, they reported in a study that the nuclear translocation was not suppressed, which was indicating that there is an additional NLS in menin (Balogh et al.,2006). Menin has a heterogeneous role as tumor suppressor in the endocrine organs, but it might be in myeloid cells a tumor promotor. Therefore, this is indicating that more studies are needed to clarify the actual role of menin (Balogh et al., 2006).

The place where the protein menin remains, is mainly in the nucleus where it interacts with activated protein 1 (AP-1) transcription factor junD, so when menin is bound to this junD, it blocks its transcription. JunD is normally inhibiting cell growth, and menin is inhibiting the activity of junD. Thus, this is the reason why tumors can arise effortlessness, when menin is mutated in MEN1(Malone et al., 2004).

2.3 Genetics

Since MEN1 is an inherited disease, the genetics are an important aspect. A child of a MEN 1 patient is having 50% chance of inheriting the MEN1 gene mutations (Falchetti et al., 2009). So, this is the reason why the inheritance is autosomal dominant, meaning that the mutated gene is dominant and lies on one of the non-sex chromosomes (MalaCards, n.d.).

Thereby, the two types MEN1 and MEN2 have different conditions because of their location on separated genes. MEN1 is located on chromosome 11, and MEN2 is located on chromosome 10, thus the type of endocrine over-activity is different in both types. Therefore, to clarify if a patient is having the syndrome, the gene location can be tested by DNA tests (Norman, 2016).

A remarkable characteristic of MEN1 is that the symptoms of the syndrome are differing per patient, and between family members. Evidence is gained by a monozygotic twin study where they looked at a twin who was suffering from MEN1 and showed different symptoms per individual. As conclusion, you inherit the gene mutation, but not the associated symptoms of the disorder (Falchetti, 2017).

2.4 The Endocrine Glands Affected by MEN1

MEN syndromes are affecting the endocrine system, but which glands are damaged, depends on the MEN type. The glands which are most affected by the MEN1 syndrome are: the parathyroid glands, pituitary gland, and the pancreas. All those three glands have different functions and show overactivity when owning the MEN1 mutation (Norman, 2016). The mechanism and secreted hormones are explained below to get insight in the symptoms and how the body is brought out of balance due to this MEN1-mutation. In figure 2, the three endocrine glands are shown including their changes due to MEN1.

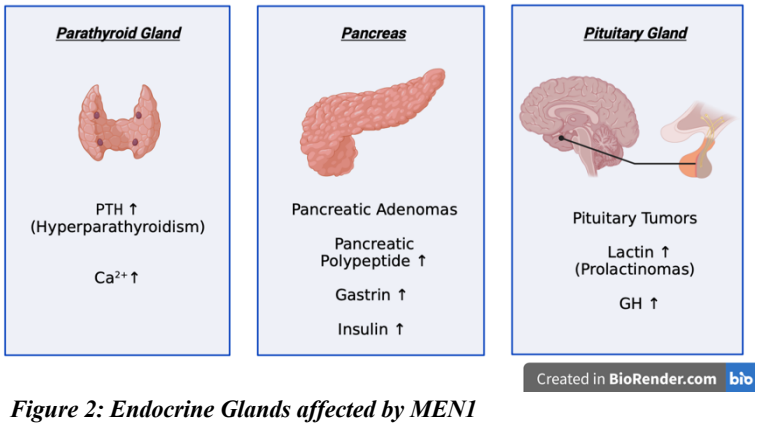

Figure 2: Endocrine Glands affected by MEN1

2.4.1 Parathyroid glands

In most of the patients inherited with MEN1, the parathyroid gland is affected. In fact, these glands are often the first glands which show overactivity. During teenage years, the over-production of the parathyroid hormone, called hyperparathyroidism, generally develops. It is stated in studies that the patients do not notice obvious symptoms until they are over the age of 30. However, 95% of the MEN1 cases are dealing with hyperparathyroidism already when being 30 years old (Norman, 2016). On the contrary, the study of Vellanki shows that when a patient is having the genetic trait for MEN1, they will

develop hyperparathyroidism later in life, at an age of 50. So, the moment where the symptoms are expressed is diverse (Vellanki, 2014).

The parathyroid glands are consisting of four small glands in the neck behind the thyroid gland, that regulate the calcium levels in the body (Norman, 2018). When these glands are showing an overactivity, and the parathyroid hormone (PTH) is overexpressed, it is ultimately bringing the calcium levels in the body up and out of balance. The parathyroid hormone is therefore also a measure technique to diagnose patients when those levels are upregulated (Malone et al., 2004).

2.4.2 Pancreas

Besides the parathyroid gland, the pancreas is the next most frequently affected gland in MEN1 patients. Small pancreatic adenomas may arise over here, and to detect those adenomas, the blood is measured to see how much pancreatic hormones are present. To further test, and get a closer look at the pancreas, a CT scan or ultrasound scan is used. These pancreatic adenomas are not resulting in symptoms and are most of the time less than 3 cm in diameter. However, sometimes it will develop into cancerous pancreatic tumors.

On the contrary, another symptom of the affected gland is the over-production of pancreatic hormones in patients. Some of the pancreatic hormones are pancreatic polypeptide, gastrin, and insulin. The overproduction of pancreatic polypeptide is not leading to any symptoms whilst overproducing gastrin can cause severe stomach ulcers and diarrhea. Thereby, high levels of insulin results in a low blood sugar and a bad health condition. This overproduction of insulin occurs most in patients under the age of 30, and the gastrin over-production occurs most after the age of 30 (Norman, 2016). The hormone gastrin is responsible for different processes like gastric mucosal growth, gastric acid secretion into the stomach, and gastric motility. The G-cells are producing and secreting gastrin, and those cells are present in the pyloric antrum, the duodenum, and the pancreas (Prosapio et al., 2021). The reason why this gastrin is malignant, is stated in the study of Ferrand and Wang. They mentioned that the gastrin gene is playing a role in the oncogenic pathway, thus active in cancers and development. In conclusion, when there is an overexpression of unprocessed, or amidated gastrins, this could lead to tumorigenesis (Ferrand & Wang, 2006).

2.4.3 Pituitary gland

The third endocrine gland which is affected by the MEN1 syndrome, is the pituitary gland. 10% to 60% of the MEN1 cases include anterior pituitary tumors and those pituitary adenomas are more usual in woman compared to men. Thereby, most of the pituitary tumors in MEN1 patients are macroadenomas, which are most of the time mixed tumors instead of monohormonal adenomas. The pituitary tumors can also cause vision problems since the tumor is oppressing the eye system. When those pituitary tumors are the starting point of MEN1, they arise at an earlier age compared to the other endocrine, intestinal, and pancreatic tumors. The dangerous thing with pituitary tumors is that they are more aggressive and invasive than others. Lastly, those tumors are regularly resistant to medical therapy, so when a patient is dealing with these kinds of tumors, it is hard to treat them (Syro et al., 2012).

One of the most common tumors in the pituitary area in MEN1 patients, are prolactinomas. Those tumors overproduce the hormone lactin which is signalling to the breasts in women for the milk production during pregnancy and breastfeeding. When women have prolactinomas, the breasts will release milk at any moment and too much lactin in the blood can also cause infertility and bone loss.

Lastly, tumors that are overproducing the growth hormone (GH) are also common in MEN1 patients. When GH is overexpressed, it can cause body tissues and bones to grow largely which can cause further problems like arthritis, the carpal tunnel syndrome, or other tumors (NIDDK, 2021).

2.5 Symptoms and Diagnosis of the MEN1 Syndrome

So, as stated before, the syndrome differs in symptoms per person, and on which age the disorder will be expressed. However, almost every MEN1 case has its parathyroid glands affected. The symptoms from parathyroid tumors are most of the time mild, and it could be the case that a patient is not aware of having the syndrome. Some other symptoms that may arise with the MEN1 syndrome are kidney stones, tiredness, muscle weakness, digestive problems, increased thirst and urination, or depression.

If the tumors are present in other endocrine glands, some signs may arise like stomach ulcers, abdominal pain, diarrhea, low glucose levels in the blood, swollen hands and feet, or acid reflux (NIDDK, 2021).

Patients who inherited the MEN1 gene, must test regularly to screen if there is overactivity in one of their endocrine glands which are associated to the syndrome. This testing means that the patient must undergo blood tests about 2 times per year, and thereby undergo some scans to screen for adenomas at an early stage. When overactivity in the endocrine glands or adenomas are noticed, treatments can be applied before it is too late.

With those blood tests, different hormone levels are measured. Firstly, the parathyroid hormone and calcium levels to identify if there is hyperparathyroidism in the patients. Secondly, prolactin, since this hormone is often over-produced by the pituitary gland in MEN1 patients. And lastly, gastrin levels are measured, because this results in stomach ulcers and is overproduced by the pancreas (Norman, 2016). Thereby, to determine which hormone is secreted by the tumor, the portal venous sampling for hormones can also be used besides blood tests (Fraker & Norton, 1989).

2.6 Demographics, Incidence and Prevalence

When looking at the demographics of a disease, it is about referring to distinct characteristics of populations, like the age, sex, environment, or genetics in the family. While observing the sex ratio in MEN1 patients, in general this is equal, so it does not matter if the patient is woman or man (Orphanet, 2020). But a person is having a higher chance to get the MEN1 syndrome when reaching a higher age, and the age of death is on adult age (Norman, 2006; Orphanet, 2020).

Furthermore, the incidence of a disease is giving information about the rate of new cases of a disease in a specific population during a specific period. The incidence proportion is about the number of new cases during the specific period, and the rate is also covering the time directly. On the other hand, the prevalence includes all cases of disease in the population, and the incidence only during a particular time era (Ford, 2020).

As early mentioned, MEN1 is a rare syndrome and occurs in 1 person in every 30,000 people. Found in databases, there is a prevalence of 1–9/100,000 for MEN1 monitored in Europe (Orphanet, 2020). Since there are a lot of individuals who carry the MEN1 mutation with them without knowing it, it is hard to be accurate with the incidence and prevalence. However, the LUMC stated that, 350 to 400 people were suffering from MEN1 in the Netherlands in 2014, so this is giving an image of the cases of MEN1 in that particular year (LUMC, 2014).

Of course, diagnosed people want to know how their future is going to look like, so what is the prognosis of the MEN1 syndrome. The bulk of the patients with Multiple Endocrine Neoplasia Type 1 live beyond the age of 65 years. When testing regularly and treating the syndrome in the right way, most patients can live a long life with good quality. However, it still needs to be mentioned that the life expectancy of MEN1 patients is not the same as the average population, which is having a mean age of death at the age of 55 years (Keller et all., 2018). It is seen in figure 3, that around the age of 50, the survival of MEN1 patients is strongly declining. The uninterrupted line stands for the mutation positive patients, so they have a mutation in the MEN1 gene, and the dotted line stands for the mutation negative patients.

The main risk for patients with MEN1 is malignancy, which is causing 30% of all deaths (Orphanet, 2020). This malignancy will arise at a higher age since it is rare before the age of 30 (Norman, 2016). Nonetheless, the over-secretion of the hormones can account for mortality and morbidity when not treated in the right way. So, the treatment success and early diagnosis of the MEN1 syndrome are prognostic factors (Orphanet, 2020).

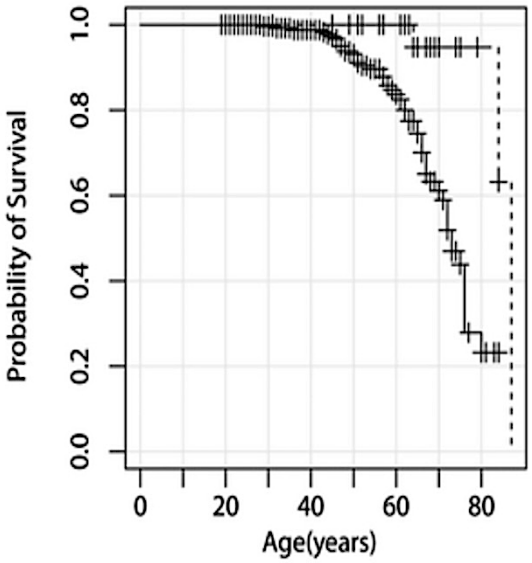

Figure 3: Survival of MEN1 mutation positive and negative patients *(De Laat et al., 2016)*

3. Genetics of the MEN1 Syndrome

The Multiple Endocrine Neoplasia Type 1 syndrome can occur in two different forms: the familial and sporadic form. In the sporadic form, only one person is affected when descending from an unaffected family. This form is rare since it is applying on 10% of all the cases. Automatically, the other 90% of the cases are belonging to the familial form, where the syndrome is inherited from family members. Nonetheless, it is hard to distinct between the sporadic and familial cases. In a few sporadic cases, it can be that there is family history, but it cannot be defined due to non-paternity, parental death, or adoption as illustration. In the familial form, so the inherited syndrome, the genetics are the starting point of MEN1, so therefore this chapter is about the genetic point of theory (Falchetti, 2017).

As declared before, patients with the MEN1 syndrome follow an autosomal dominant inheritance pattern, which means that the children of diagnosed patients have 50% chance of receiving this MEN1 gene mutation (Falchetti et al., 2009). The symptoms of the syndrome are differing per affected person, as well in family members, as in MEN1 monozygotic twins. So, you inherit the MEN1 gene mutation, but not the corresponding symptoms (Falchetti, 2017).

3.1 Genomic Locations and Mutations

Which is important in genetics, is the genomic location since this gene location is decisive for the type of disorder you will develop, and the symptoms that will arise (Norman, 2016). The MEN1 gene is based on chromosome number 11q13, which contains 10 coding parts of the gen, also known as exons with a coding region of 1830 base pairs. Those exons encode the 610-amino acid protein menin, which is explained previously. Menin is expressed and especially present in non-dividing cells as a nuclear protein (Malone et al., 2004). In total, there are 1336 mutations demonstrated, consisting of 1133 germline mutations and 203 somatic mutations, and the 1133 germ-line mutations are distributed throughout the 1830 bp coding region. The type of mutations which is most common, are frameshift deletions or insertions with a percentage of 41%. The most common spots for mutations are codons 83, 84, 209-2119, and 514-516 (Lemos & Thakker, 2008; Malone et al., 2004).

It still needs to be investigated why between 5% and 10% of the affected patients are not having mutations within the coding region of the MEN1 gene. These individuals probably have whole gene deletions, promotor mutations, or untranslated regions (Lemos and Thakker, 2008). Meanwhile, in another study, it is shown that around 33% of individuals who lack the mutations in the coding region, have enormous mutations involving entire exons (Cavaco et al., 2002).

3.2 Diagnosis of Inheritance

To decide if an individual has inherited the MEN1-mutation, a genetic test must be done. Moreover, when the disease occurred in the family history, it is possible for all ages to undergo a predictive genetic testing procedure, for which only a single blood sample is needed. The DNA from this blood sample is tested for the existence of a deviant MEN1 gene. Thereafter, when a particular person contains an abnormal MEN1 gene, the individual receives a positive result. So, automatically when having a negative result, there is no MEN 1 present, or it is not possible to pass MEN 1 to their offspring (Norman, 2016).

4. Parathyroid hormone (PTH)

Previously stated, one of the glands that is almost always affected in MEN1 patients, is the parathyroid gland. The overproduction of the parathyroid gland, called primary hyperparathyroidism, is the most common and earliest sign of the MEN1 disease. So, because the parathyroid hormone is often overproduced in the patients, this hormone has a big role in the Multiple Endocrine Neoplasia Type 1 syndrome (Malone et al., 2004).

4.1 Primary Hyperparathyroidism

In 90% of the MEN1 patients primary hyperparathyroidism is the initiation of the disorder (Malone et al., 2004). The overproduced hormone in hyperparathyroidism, the parathyroid hormone (PTH), is the main regulator of the calcium levels in the human body. When there is an overproduction of PTH from the parathyroid glands, hypercalcemia will arise where the calcium levels in the blood are too high. Again, with this hyperparathyroidism, there is no preference for a particular sex (Mackenzie-Feder et al., 2011). A person can have primary hyperparathyroidism for years without having symptoms, or they can experience nausea, vomiting, weakness, fatigue, high blood pressure, bone thinning, or kidney stones, which they do not directly relate to the disease (Vellanki, 2014).

Hyperparathyroidism is easy to identify since the glands are overproducing the parathyroid hormone, and this hormone level can be measured without any problems. Under normal conditions, there will be a normal calcium level and normal parathyroid hormone level. Thereby it is also a normal condition when calcium and PTH are having an inversely proportional relationship. When talking about a bad condition, the PTH level is elevated together with an elevated serum calcium (Norman, 2018). Besides, it is even possible that an elevated PTH level is not caused by primary hyperparathyroidism, but by other causes like chronic kidney disease, lack of vitamin D, medications, or mutations of the calcium sensing receptor gene (Mackenzie-Feder et al., 2011).

To measure those elevated PTH levels, immunoradiometric (IRMA) and immunochemiluminescent assays are performed. These assays measure both the 1-84 amino acid sequence of the parathyroid hormone, and other large fragments (Mackenzie-Feder et al., 2011). Another manner to identify hyperparathyroidism, is to measure the calcium level in the urine over a period of 24 hours. When the kidneys are working well, they will filter the calcium to clean the body of the huge amount, which will result in a high calcium in the secreted urine. However, it must be mentioned that this technique is an indirect measure of the parathyroid activity, so it is only accurate in 25% to 40% of the cases. Concluding, the best diagnosis is to show that there is either an elevated parathyroid hormone level as well as an elevated serum calcium (Norman, 2018).

4.2 Physiology of Calcium Regulation

Bound to the parathyroid hormone, is the calcium regulation, which is important for processes as cell signalling, muscular functions, hormone regulation, bone metabolism, and cell signaling. When PTH is released, it is stimulating the reabsorption of calcium in the kidneys, and this releases skeletal calcium stores, so phosphate and calcium are released in the blood. Thereby, PTH is carrying an increased 1,25-dihydroxy-vitamin D production and calcium reabsorption from the gastrointestinal tract, by upregulating the 1-α-hydroxylase levels.

In the chief cells of the parathyroid glands, calcium-sensing receptors (CaSRs) are responding to the levels of ionized calcium in the extracellular space. This receptor is regulating the release of the parathyroid hormone when those ionized calcium levels are out of balance (Mackenzie-Feder et al., 2011).

5. Treatment of the MEN1 Syndrome

When dealing with endocrine tumors, it can be life-threatening since it has a disproportionate secretion of hormones, and thereby the phenomenon that neoplasm is cancerous. This neoplasm is also the case in the MEN1 syndrome, but the problems caused by MEN1 can generally be controlled when making use of the right treatments. On the contrary, it is not possible to completely cure MEN1 since the malfunctioning gene is present in every cell.

It could be that there will be developed a drug in the future, which is preventing the endocrine gland overactivity related to Multiple Endocrine Neoplasia Type 1. However, to stay realistic, people with MEN1 mutations will have to do regular tests to early diagnose the syndrome and treat it. This treatment will almost always contain of surgical removal of the adenomas which show over-activity. On a lot of treatments, risks are bound, so patients as well as doctors are often considering if a treatment is worth the quality of life (Norman, 2016). Thereby, when fewer than three endocrine glands are removed at the initial step, the bigger the chance on a recurrence of hyperparathyroidism (Lambert, 2005).

5.1 Treatment of Primary Hyperparathyroidism

Beginning with the treatment in patients with hyperparathyroidism, who have the choice between doing nothing or undergo surgery to remove the diseased parathyroid gland. When a patient is having a mild form of the primary hyperparathyroidism, doctors will not recommend undergoing the surgery since this surgery is a big challenge, and the patients must realize that the parathyroid disease will get worse because it will not disappear on its own. On the other hand, patients must realize that when hyperparathyroidism is caused by a tumor which comes from one of the parathyroid glands, and when waiting this will increase in size. The age of the patients does not matter for the surgery since the new techniques of the parathyroidectomy are able to help patients of any age. Besides, this procedure is fast because it makes use of a local anesthesia, so the patients can return home in a couple of hours (Norman, 2018).

The minimally invasive radioguided parathyroid surgery (MIRP) is a way to remove the overactive parathyroid tumor. First, the overproducing parathyroid gland is made radioactive to differentiate it from all the other parts in the neck. Thereafter, the surgery will take place only on the places where necessary, using a small incision. This operation can be accomplished using a local anesthesia, instead of a general anesthesia, but the patient is given some sedative medications in the veins to lower the awareness. During the surgery, a hand-held radiation detecting probe is used into the incision, to find the radioactive parathyroid gland. This radioactivity is valid for 2 to 4 hours, so in this time range, the whole surgery must take place. The operation can be done through a 1-in incision in 25 minutes and the next step is to dissect and remove the overactive parathyroid tumor. Finally, the last thing to be done, is to measure the radioactivity in the parathyroid tumor since this is giving information about if the patient is cured from the MEN1 syndrome (Norman, 2014).

For the patients who are not able or not want to do the parathyroid surgery, there is an opportunity to make use of medical treatment. Studies did a lot of investigations in how to treat the primary hyperparathyroidism in a medical way. One study investigated how the components cinacalcet and bisphosphonates are having effect on reducing the hyperparathyroidism effects since both compounds are normally lowering the calcium levels in the body. In this study, they showed that bisphosphonates have a short-lived effect, for less than six months, on the plasma calcium, but it works on the bone mineral density (BMD). On the other hand, cinacalcet is having a long-term effect on the plasma calcium but is not improving the bone mineral density (Leere et al., 2017).

5.2 Treatment of Islet Cell Tumors in the Pancreas

Secondly, the treatment for patients with islet cell tumors in the pancreas, for which the decisive diagnosis of the hormonal syndrome is done biochemically. After this, the islet cell neoplasm is localized radiographically to prepare the individual for the operation. This surgery is done to precisely map the extent of the disease and thereby to eliminate the tumor. Eventually this will correct the hormonal balance and extract the change that tumors will become malignant again. When a complete or nearly complete resection is possible in the patient, this resection should enclose the metastatic disease, where

the cancer can spread to other parts of the body. However, this operation is only performed if the death rate of the surgery is not that high. When the death rate is high, performing the operation is irrelevant since the progression rapidity of the cancerous islet cell carcinomas is commonly not high (Fraker & Norton, 1989).

Nevertheless, the patients with islet cell tumors associated with the MEN1 syndrome should be identified thoroughly and handled differently because those patients will have multiple tumors and they could have malignant carcinomas. When the pancreatic neoplasms are large, around 3 centimeters, this should be removed anyway since 50 percent of those neoplasms is cancerous (Arnold, 2022).

Patients who are suffering from the Zollinger-Ellison syndrome have often small tumors, which makes it hard for a doctor during the surgery to cover all the tumors and get them out of the body. Therefore, patients with MEN1 are not recommended to undergo a surgery for the Zollinger-Ellison syndrome. On the contrary, when a tumor is that big, a surgery will be performed because this can be targeted more easily. Thereby, since in the Zollinger-Ellison syndrome the gastric acids are overproduced, doctors can treat patients with PPIs, proton pump inhibitors, which are lowering the acid amount in the stomach (Arnold, 2022).

5.3 Treatment of Pituitary Tumors

Lastly, to treat patients the pituitary tumors, the goal is to minimize the volume of the tumor, to normalize the hormone hypersecretion and keeping the function of the pituitary as what it should be. The treatments that are used to fulfill those goals, are surgeries, medication, and radiotherapies.

The medication that is used are agonists for dopamine, somatostatin analogs, and antagonists for the growth hormone receptors. To make a choice between the treatments, information is needed about which hormone is overproduced in the patient, the size of the tumor and how invasive this tumor is. Besides, doctors have a look at if there are complications when performing a surgery, or if there are problems in the visual area because of tumor suppression. Of course, the patient is asked for a preferred treatment method when there are several opportunities.

This treatment is not different for patients with sporadic pituitary tumors, or MEN1-associated pituitary tumors. The status of treatment options for the pituitary tumors is that a different treatment is possible, but not currently announced (Syro et al., 2012).

6. Advice for MEN1 Patients and their Family

In short, patients with the MEN1 syndrome can have damaged parathyroid glands, pituitary glands, or a damaged pancreas. Those different glands are overproducing several hormones which can bring the body in bad health conditions. In almost every MEN1 case, hyperparathyroidism is present, which will cause elevated parathyroid hormone and calcium levels in the body. Since the disorder has an autosomal dominant inheritance pattern, children of MEN1 patients have a 50% chance of inheriting this MEN1 mutation.

To come at an answer on the question how MEN1 patients and their family should handle with the disease, some advice is made, covering the affected endocrine glands, their symptoms and treatments. The MEN1 patients are a small portion of the whole population with endocrine disorders. But disorders which have similarities with Multiple Endocrine Neoplasia Type 1 are those with an overactivity in the parathyroid gland, pancreas, and pituitary gland. When an individual is having overactivity in 2 of more endocrine glands, this person should be tested for MEN1 (Norman, 2016).

Individuals who have inherited the MEN1 gene need to screen for the endocrine gland overactivity regularly. About every year, these individuals should test their blood and early diagnose overactivity of the glands, or adenomas. The sooner they get a diagnose, the sooner they can treat the disorder. The reason why regularly blood testing is recommended, is because sometimes the pancreatic adenomas will become malignant over the years. Nonetheless, before the age of 30 it is rare that the pancreas is becoming malignant (Norman, 2016). Thereby, for patients with the MEN1 syndrome, it is also advised to undergo biochemical screening for the pituitary tumors and MRI screening of the pituitary gland every 3 to 5 years (Keller et al., 2018). When people who live in surroundings where MEN1 genetic testing is not accessible, it will be offered when it can be demonstrated that there is a strong family history of MEN1. (Norman, 2016).

Sometimes, it is the case that a person does not know there is a MEN1 history in the family. This can be the case when there is non-paternity, parents died, or those individuals are adopted. Thereby, we also deal with the circumstances that the symptoms are really varying among people, so some live to an old age with hardly any health problems, and some are the victims soon with a lot of health problems. The symptoms like stomach ulcers, tiredness, and kidney stones, are also very common among people who are not having MEN1. So, MEN1 may be not recognized in family, or experienced by the patient, despite it is present (Norman, 2016).

So, as a conclusion, patients with family history, or symptoms that are MEN1 associated, should regularly test their blood, and undergo screens, to limit the damage to a certain extent. With several treatments, the glands can be recovered, and the hormone balance in the body will be restored. Still, when a patient is diagnosed, it is important for the offspring to also undergo genetic tests to know if they have inherited the MEN1 mutation. At the end, when having the Multiple Endocrine Neoplasia Type 1 Syndrome, the symptoms are mild, and the surgery is risky, doctors are discouraging treatments against the MEN1 syndrome since the quality of life could be possibly destroyed.

References

1. Agarwal, S. K., Guru, S. C., Heppner, C., Erdos, M. R., Collins, R. M., Park, S. Y., Saggar, S., Chandrasekharappa, S. C., Collins, F. S., Spiegel, A. M., Marx, S. J., & Burns, A. (1999). Menin Interacts with the AP1 Transcription Factor JunD and Represses JunD-Activated Transcription. Cell, 96(1), 143–152. https://doi.org/10.1016/s0092-8674(00)80967-8
2. Arnold, A. (2022, 14 februari). Multiple endocrine neoplasia type 1: Treatment. UpToDate. Geraadpleegd op 11 april 2022, van https://www.uptodate.com/contents/multiple-endocrine-neoplasia-type-1-treatment
3. Balogh, K., Rácz, K., Patócs, A., & Hunyady, L. (2006). Menin and its interacting proteins: elucidation of menin function. Trends in Endocrinology & Metabolism, 17(9), 357–364. https://doi.org/10.1016/j.tem.2006.09.004
4. Boro, H., Kubihal, S., Arora, S., Kubihal, V., & Tandon, N. (2020). Multiple Endocrine Neoplasia Type 1 Syndrome: A Case Report and Review of Literature. Cureus. https://doi.org/10.7759/cureus.12073
5. Cavaco, B. M., Domingues, R., Bacelar, M. C., Cardoso, H., Barros, L., Gomes, L., Ruas, M. M. A., Agapito, A., Garrão, A., Pannett, A. A. J., Silva, J. L., Sobrinho, L. G., Thakker, R. V., & Leite, V. (2002). Mutational analysis of Portuguese families with multiple endocrine neoplasia type 1 reveals large germline deletions. Clinical Endocrinology, 56(4), 465–473. https://doi.org/10.1046/j.1365-2265.2002.01505.x
6. De Laat, J. M., Van der Luijt, R. B., Pieterman, C. R. C., Oostveen, M. P., Hermus, A. R., Dekkers, O. M., De Herder, W. W., Van der Horst-Schrivers, A. N., Drent, M. L., Bisschop, P. H., Havekes, B., Vriens, M. R., & Valk, G. D. (2016). MEN1 redefined, a clinical comparison of mutation-positive and mutation-negative patients. BMC Medicine, 14(1). https://doi.org/10.1186/s12916-016-0708-1
7. Falchetti, A. (2017). Genetics of multiple endocrine neoplasia type 1 syndrome: what's new and what's old. F1000Research, 6, 73. https://doi.org/10.12688/f1000research.7230.1
8. Falchetti, A., Marini, F., Luzi, E., Giusti, F., Cavalli, L., Cavalli, T., & Brandi, M. L. (2009). Multiple endocrine neoplasia type 1 (MEN1): Not only inherited endocrine tumors. Genetics in Medicine, 11(12), 825–835. https://doi.org/10.1097/gim.0b013e3181be5c97
9. Ford, G. (2020, 6 november). Prevalence vs. Incidence: what is the difference? Students 4 Best Evidence. Retrieved March 29, 2022, from https://s4be.cochrane.org/blog/2020/11/06/prevalence-vs-incidence-what-is-the-difference/
10. Fraker, D. L., & Norton, J. A. (1989). The Role of Surgery in the Management of Islet Cell Tumors. Gastroenterology Clinics of North America, 18(4), 805–830. https://doi.org/10.1016/s0889-8553(21)00443-x
11. Keller, H. R., Record, J. L., & Lall, N. U. (2018). Multiple Endocrine Neoplasia Type 1: A Case Report With Review of Imaging Findings. Ochsner Journal, 18(2), 170–175. https://doi.org/10.31486/toj.17.0019
12. Lambert, L. A. (2005). Surgical Treatment of Hyperparathyroidism in Patients With Multiple Endocrine Neoplasia Type 1. Archives of Surgery, 140(4), 374. https://doi.org/10.1001/archsurg.140.4.374
13. Leere, J. S., Karmisholt, J., Robaczyk, M., & Vestergaard, P. (2017). Contemporary Medical Management of Primary Hyperparathyroidism: A Systematic Review. Frontiers in Endocrinology, 8. https://doi.org/10.3389/fendo.2017.00079
14. Lemos, M. C., & Thakker, R. V. (2008). Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. Human Mutation, 29(1), 22–32. https://doi.org/10.1002/humu.20605
15. LUMC. (2014, 18 augustus). Multipele Endocriene Neoplasie (MEN) I syndroom | LUMC. Retrieved March 29, 2022, from https://www.lumc.nl/patientenzorg/praktisch/patientenfolders/multipele-endocrine-neoplasie-MEN-I-syndroom

16. MacKenzie-Feder, J., Sirrs, S., Anderson, D., Sharif, J., & Khan, A. (2011). Primary Hyperparathyroidism: An Overview. International Journal of Endocrinology, 2011, 1–8. https://doi.org/10.1155/2011/251410
17. Malone, J. P., Srivastava, A., & Khardori, R. (2004). Hyperparathyroidism and multiple endocrine neoplasia. Otolaryngologic Clinics of North America, 37(4), 715–736. https://doi.org/10.1016/j.otc.2004.02.005
18. Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. 6 25 57 61. (z.d.). MalaCards. Retrieved March 29, 2022, from https://www.malacards.org/card/multiple_endocrine_neoplasia_type_i?search=men%201-syndrome
19. Multiple Endocrine Neoplasia Type 1. (2021, 9 december). National Institute of Diabetes and Digestive and Kidney Diseases. Geraadpleegd op 8 april 2022, van https://www.niddk.nih.gov/health-information/endocrine-diseases/multiple-endocrine-neoplasia-type-1
20. Norman, J., MD. (2014, 27 mei). How Minimally Invasive Radioguided Parathyroid Surgery (MIRP) Is Performed. EndocrineWeb. Retrieved 5 April, 2022, from https://www.endocrineweb.com/conditions/hyperparathyroidism/how-minimally-invasive-radioguided-parathyroid-surgery-mirp-performed
21. Norman, J., MD. (2018, 20 november). Hyperparathyroidism Diagnosis and Treatment. EndocrineWeb. Retrieved 5 April, 2022, from https://www.endocrineweb.com/conditions/hyperparathyroidism/hyperparathyroidism-diagnosis-treatment
22. Norman, J., MD. (April 13, 2006). Multiple Endocrine Neoplasia Type 1. EndocrineWeb. Retrieved March 29, 2022, from https://www.endocrineweb.com/conditions/pituitary-disorders/multiple-endocrine-neoplasia-type-1
23. Öberg, K. (2013). The Genetics of Neuroendocrine Tumors. Seminars in Oncology, 40(1), 37–44. https://doi.org/10.1053/j.seminoncol.2012.11.005
24. Orphanet: Multiple endocrine neoplasia type 1. (2020). Orphanet. Retrieved March 29, 2022, from https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=652
25. Prosapio JG, Sankar P, Jialal I. Physiology, Gastrin. [Updated 2021 Mar 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534822/
26. Strewler, G. J. (2000). The Physiology of Parathyroid Hormone–Related Protein. New England Journal of Medicine, 342(3), 177–185. https://doi.org/10.1056/nejm200001203420306
27. Syro, L., Scheithauer, B., Kovacs, K., Toledo, R., Londoño, F., Ortiz, L., Rotondo, F., Horvath, E., & Uribe, H. (2012). Pituitary tumors in patients with MEN1 syndrome. Clinics, 67(S1), 43–48. https://doi.org/10.6061/clinics/2012(sup01)09
28. Vellanki, P., MD. (2014, 6 oktober). Multiple Endocrine Neoplasia: MEN Types 1 and 2. EndocrineWeb. Retrieved March 30, 2022, from https://www.endocrineweb.com/conditions/multiple-endocrine-neoplasia-men-types-1-2
29. Walls, G. V. (2014). Multiple endocrine neoplasia (MEN) syndromes. Seminars in Pediatric Surgery, 23(2), 96–101. https://doi.org/10.1053/j.sempedsurg.2014.03.008