Overview of Multiple Endocrine Neoplasia Type 2A

by Mary Brooke Maher, M.D.

Description of MEN2A

Multiple Endocrine Neoplasia Type 2A (MEN2A) is a rare autosomal dominant inherited condition causing tumors in multiple endocrine glands, specifically the thyroid, adrenal glands, and parathyroids.

The Three Main Tumor Types of MEN 2A

1. Medullary Thyroid Cancer (MTC)
2. Pheochromocytoma (PHEO)
3. Parathyroid adenomas/hyperplasia

Diagnosis of MEN2A

You can be diagnosed with MEN2A one of the following ways:

1. Having 2 of the 3 tumors types (MTC, PHEO, and hyperparathyroidism) in a single patient
2. Having 1 tumor type in the patient and a family history of MEN2A and/or family history of the tumor types associated with MEN2A (e.g. a patient with MTC whose parent had a PHEO and sibling had hyperparathyroidism)
3. Genetic testing showing a RET mutation

*Please note that 1 and 2 above are CLINICAL diagnoses and 3 is a genetic confirmation of diagnosis. In a small percentage of patients, CLINICALLY there is a diagnosis of MEN2A but the genetic test is negative. If this happens, you still have MEN2A and should be treated and monitored as such.

Medullary Thyroid Cancer (MTC)

Medullary thyroid cancer (MTC) occurs in nearly 100% of all MEN2A patients at some point in their lifetime. It has been seen as early as 6 months of age. MTC is cancer that arises from the C-cells of the thyroid. The C-cells are NOT the part of your thyroid that is tested in "thyroid function tests." You can have MTC and have NORMAL thyroid function tests. The C-cells are separate and make a hormone called calcitonin. In MEN2A patients calcitonin will be increased either from MTC

or from its precursor condition called C-cell hyperplasia. MTC can spread to the surrounding lymph nodes or to distant sites within the body.

Symptoms of MTC

*Often asymptomatic which is why testing for MEN2A and monitoring after diagnosis are so important
A mass (lump or bump) in your neck
Diarrhea (when calcitonin level are very high)
Occasionally neck pain
Hoarseness or difficulty swallowing (if MTC has damaged surrounding nerves)

Tests to Diagnosis MTC

Blood Tests

Calcitonin
Carcinoembryonic Antigen (CEA) – this can also be a marker of MTC and how aggressive the MTC is behaving
*All patients with MTC should be tested for the RET mutation

Imaging

Ultrasound of the neck
Possibly a CT and/or MRI scan

Other Tests

Possibly a fine needle biopsy of thyroid
A physical exam including a physical exam of your neck

Treatment of MTC

The first and preferred treatment for MTC is surgery to remove the thyroid gland and maybe the lymph nodes surrounding the thyroid too. Surgery may occur after diagnosis of MTC or surgery can be preventative in patients diagnosed with MEN2A. Depending on the RET mutation a patient has, surgery may be recommended at a very young age or may be delayed until puberty or later. Discuss your specific mutation in detail with your doctor to determine the best time for you and your family to have your thyroid removed.

There are some risks to the surgery, which should be discussed with your doctor. The main one is damage to the recurrent laryngeal nerve (RLN), which is what makes your vocal cords work. If the RLN is damaged, you can have a range of symptoms from being slightly hoarse to being very hoarse, difficultly swallowing, and choking. Ask your doctor what steps he or she takes to prevent damage to the RLN during surgery. RLN damage usually improves in 8-12 weeks, but can be

permanent in some patients. If permanent, there are options available to improve vocal cord function.

If surgery is not possible or is not enough because MTC is widespread, there are some other forms of treatment. Some doctors give radioactive iodine (RAI), which only kills the functional part of the thyroid (not the C-cells that cause MTC). The thought is that in killing any remaining functional thyroid, the C-cells next to it might be killed by accident just from being so close. Not every doctor recommends this and it isn't used except in special circumstances. Talk to your doctor about what he or she recommends.

Patients with MTC that has spread to other parts of their body may be placed on tyrosine kinase inhibitors (TKIs). RET mutations affect tyrosine kinase receptors (see genetics section below). These drugs are only used in advanced MTC. Ask your doctor about TKIs and whether or not they are an option for you.

After Surgery

You will have to take thyroid replacement hormone (levothyroxine) for the rest of your life. It can take some time to get your medication level just right, so have open conversations with your endocrinologist about how you are feeling. A blood test to check your thyroid-stimulating hormone (TSH) should be checked about a month after your surgery and then every few months thereafter in order to evaluate whether your levothyroxine dose is working for you. Once you find the right dose for your body, you won't have to get your TSH checked as often.

There can also be damage or incidental or intentional removal of the parathyroid glands. You should be monitored for too little calcium in your blood (hypocalcemia) after surgery. Your doctor will do this by checking calcium and parathyroid hormone (PTH) levels. You may need to take calcium and vitamin D supplements for a while after your surgery. (See more on this in the hyperparathyroidism section below)

After surgery you will also need your calcitonin and CEA checked at intervals determined by your surgeon. The "doubling time" of your calcitonin and CEA may also need to be examined. Doubling time is the amount of time it takes for your blood calcitonin and/or CEA levels to double.

Pheochromocytoma (PHEO)

Roughly half of MEN2A patients develop pheochromocytomas (PHEO). Pheochromocytomas are tumors in your adrenal glands. You have two adrenal glands and they sit right on top of your kidneys. The adrenal gland has two parts, the cortex around the outside and the medulla in the middle. The medulla makes your fight or flight hormones called epinephrine (E) and norepinephrine (NE) - you may have heard of them as adrenaline and noradrenaline. PHEOs are tumors of the

adrenal medulla. While a PHEO is usually not cancerous, it can be deadly. The epinephrine and norepinephrine it secretes can cause wild swings in your blood pressure and pulse resulting in stroke and even sudden death.

Because of the swings in blood pressure and heart rate, surgery and anesthesia are very dangerous if you have a PHEO. Therefore, before ANY surgical procedure, a PHEO must be ruled out. If a PHEO is detected, the PHEO should be removed first. Then the other surgery can take place at a later date. **So if you have MEN2A, you need to make sure you are tested for a PHEO prior to ANY surgery for ANY cause.**

Females with MEN2A should be screened for PHEO prior to a planned pregnancy. In the case of an unplanned pregnancy, PHEO should be screened for as soon as possible. **Pheochromocytomas during pregnancy are very dangerous for both the mother and the baby and can result in death of both.** It is generally recommended that a PHEO in a pregnant patient be treated prior to the 3rd trimester of pregnancy. You may need to have a c-section rather than giving birth vaginally. Please discuss pregnancy with your endocrinologist and endocrine surgeon and tell your obstetrician about MEN2A and your PHEO risks.

Symptoms

Racing heart rate
Headache
Sweating
Flushing
Heart palpitations
Trembling
Shaking
Depression
Anxiety
Pale appearance
High blood pressure (either episodically or constantly)

These are just some of the symptoms of PHEO. They generally occur in episodes and the patient is symptom free between episodes. Patients sometimes say that these episodes feel like a panic attack. **In MEN2A individuals, however, a PHEO can be totally asymptomatic with normal blood pressure**. So again, it is very important to get tested for MEN2A and to be monitored yearly with lab work so that if you do develop a pheochromocytoma, it can be treated early.

Tests

1. Plasma fractionated metanephrines (if already diagnosed with MEN2A)

The first test for a PHEO if you have already been diagnosed with MEN2A is plasma fractionated metanephrines and normetanephrines. This is a blood test. If it is negative, you do not have PHEO (at this time). If it is positive, then you need to be further evaluated for a PHEO. It could be a false positive result. False positive means that you test positive but you don't really have a PHEO. Therefore, a positive plasma meta/normetanephrine test needs to be retested by other means. One way to do that is to repeat the blood test but have the patient lie quietly with the needle inserted in their vein for 30 minutes before drawing blood. This allows time for your natural fight or flight hormones (that are released when someone pokes you with a sharp needle) to return to normal.

2. 24-hour urine fractionated metanephrines and catecholamines (if you have NOT been diagnosed with MEN2A already or if you had a positive plasma test)

The other follow-up test for a positive plasma test (or the first test if you have not been diagnosed with MEN2A already) is a 24-hour urine collection for fractionated metanephrines and catecholamines. During these tests, you collect your urine over a full 24-hours. Please confirm with your doctor and laboratory the exact instructions for collection. Often these urine samples need to be refrigerated or have a preservative added to them either before or after collection. Different labs use slightly different tests so be sure that you know your lab's instructions. Also ask if any foods or medications may change the results of this test. If so, should you avoid those foods/meds and for how long before testing?

If your urine test is normal, then no further testing needs to be done at this time unless you are having spells of headache, high blood pressure, sweating, heart palpitations, etc. In a patient having spells, the urine collection should be repeated during a spell. Ask your doctor how to collect urine during a spell.

If the 24-hour urine test is positive for a PHEO, then retesting and/or additional imaging using either CT or MRI or both is recommended. Sometimes, you can have a PHEO but it doesn't show up on CT or MRI. In this case, you may need other forms of imaging in order to see where your tumor is located. Ask your doctor about other imaging.

Treatment

Treatment for PHEO is surgical removal of the adrenal medulla or adrenal gland. Currently, it is recommended that only the affected gland be removed preserving the other gland and adrenal function for the time being. In MEN2A, however, the second adrenal will likely develop a PHEO as well. Sometimes, patients already have a PHEO in each adrenal and both adrenal glands must be removed. There is the possibility of preserving the cortex of the adrenal gland in some cases. Talk to your doctor about whether surgery will spare your adrenal cortex or not and why.

Patients with a PHEO must undergo alpha-blockade before surgery. Alpha-blockers (and sometimes beta-blockers) are medicines used to help stabilize blood pressure. It is critical that you have your blood pressure controlled prior to surgery for a PHEO. Ask about what will be done to prepare you for surgery and keep you healthy during surgery. Ask how much experience your anesthesiologist (the doctor who puts you to sleep in the operating room) has with adrenal surgeries and PHEO.

After Surgery

The alpha-blockade will not need to be continued after successful removal of the PHEO.

If you had both adrenal glands removed without sparing the adrenal cortex, you will permanently need to take glucocorticoid and mineralocorticoid replacements. Glucocorticoid and mineralocorticoid (together called corticosteroids) are made by the adrenal cortex and are essential for life. Your levels of these steroids will need to be monitored closely for the rest of your life. Without enough corticosteroids you can have an adrenal crisis. Should you get very sick or become injured, medical staff will need to know that you don't have adrenal glands and that you need corticosteroids. Without this you could quickly go downhill. **You will need a medic alert bracelet or necklace stating that you are on corticosteroids and have no adrenal glands.**

The epinephrine and norepinephrine that your PHEO was making are not necessary for life and do not need to be replaced with medication.

Hyperparathyroidism

You have four parathyroid glands. Each normal gland is about the size of a grain of rice and they sit behind your thyroid gland. Hyperparathyroidism is a disease in which the parathyroid glands make too much or make inappropriate parathyroid hormone (PTH). This can be from parathyroid adenomas (non-cancerous tumors) or parathyroid hyperplasia (non-cancerous overgrowth). Usually too much PTH causes the blood calcium level to become increased. PTH tells your body to take calcium out of your bones and put it in your blood stream. Once in your blood stream, your body then works to put calcium other places that it shouldn't be like in the walls of your blood vessels, heart, kidneys, muscles, ligaments, brain, etc. Your body also works really hard to get rid of calcium using your kidneys. This can cause calcium levels in your urine to increase making you have to urinate more often than normal. Urinating often can make you more thirsty than usual. Some patients get kidney stones.

Symptoms

Classic Symptoms:
Moans – feeling tired all the time
Groans – gastrointestinal issues like constipation, acid reflux, loss of appetite, peptic ulcers, nausea, and more rarely pancreatitis
Bones – bone pain, which can be very severe
Stones – kidney stones

Psychiatric overtones – associated confusion, forgetfulness, depression, anxiety, and irritability

Other symptoms:
"Thrones" – because increased urination makes you visit the "porcelain throne" often
Just not feeling right
Feeling old
Muscle weakness
Trouble concentrating
Feeling detached from your surroundings
Feeling like you just can't get your brain to work.
Headaches
Heart palpitations
Atrial fibrillation
Osteopenia (too little calcium in your bones)
Osteoporosis (way too little calcium in your bones)
Stroke

***You do NOT have to have a really high calcium to have symptoms.** A calcium of 10.6 can cause symptoms equally as bad as a calcium of 13. If your doctor says your calcium isn't high enough to cause symptoms, then consider getting a second opinion. Only under certain circumstances (like prior surgery in the neck) is it reasonable to just watch an elevated calcium. There is no "magic number" that your calcium needs to reach before surgery is an option for you. So if your surgeon says they won't operate until your calcium is 12, you may need a second opinion. **If you have hyperparathyroidism, surgery is most likely an option for you.**

Tests

Blood Tests:
Serum calcium (either corrected for albumin or ionized calcium)
Intact PTH
***Your PTH does NOT have to be high! It only has to be "inappropriate."**
For example, if your calcium is 10.6 and your PTH is 45, you have hyperparathyroidism because at a calcium of 10.6 your PTH should be close

to zero. So a PTH of 45 is "inappropriate" and indicative of parathyroid disease.

Urine Tests:

24-urine collection for calcium and creatinine – to see if too much calcium is leaking into your urine

Imaging Tests:

Sesta-MIBI scan – to localize your parathyroid tumors**. Please note that a negative sestamibi scan does NOT mean that you don't have a tumor.** Labs are the only way to diagnose hyperparathyroidism. Sestamibi scans are often show nothing even when large tumors are there.

Ultrasound of the neck – to localize parathyroid tumors

Other imagining studies if your doctor feels it is necessary

Treatment

Treatment for hyperparathyroidism is surgery to remove the diseased glands. Discuss your surgeon's plan in detail. Ask if your surgeon plans to examine all four glands or only the diseased gland (if you have MEN, you want a surgeon to visually inspect all your parathyroid glands), whether only enlarged glands will be removed, if intraoperative PTH levels will be monitored, and how will your surgeon protect the function of your recurrent laryngeal nerve (RLN). The RLN can be damaged during parathyroid surgery just as it can during thyroid surgery.

Sometimes, it is necessary to remove all 4 parathyroid glands. If this happens, you will need to have one of them put somewhere else in your body. This is called an autograft. Most surgeons choose the non-dominant forearm. This site is chosen because it is easy to access. In the future, your surgeon can easily get to the gland in the forearm to shave it down and make it smaller should it start to overproduce PTH again. Discuss your surgeon's plan for this and discuss what happens if the autograft fails. Also, ask your surgeon how often they perform parathyroid surgery, as you want someone VERY experienced.

After Surgery

After surgery you should be monitored for calcium and PTH levels. You may experience low blood calcium (hypocalcemia) after surgery. This is usually temporary and is treated with a calcium supplement. Sometimes no parathyroid tissue is left (permanent) or the remaining tissue is in shock and not making PTH yet (transient). This means the levels of PTH will be zero or near zero (called hypoparathyroidism) and this can make your calcium too low. In the case of hypoparathyroidism, you must take calcium and vitamin D in order to keep your blood calcium levels normal. **Too little calcium in the blood can lead to a life threatening condition called tetany.** Early symptoms of tetany are tingling and

numbness of the fingers and toes and around the mouth. It can progress to full body muscle cramps and death if not promptly treated. If you are permanently hypoparathyroid because you have no parathyroid glands left, you will have to take calcium and vitamin D for the rest of your life. Not getting these supplements can be dangerous to your health. **Therefore, if you are permanently hypoparathyroid, you must get a medic alert bracelet.**

You should also know that in an emergency, it is difficult to give calcium through a regular IV line and may damage your veins. Thus, you may need a different type of IV access like a central line in order to get calcium in an emergency.

Other Conditions Seen in Some MEN2A Patients

Cutaneous Lichen Amyloidosis (CLA)

Some patients have very itchy skin on their back between the shoulder blades. Overtime this skin can become darker than the surrounding skin. Itching may improve with sun exposure and worsen with stress. This condition is called cutaneous lichen amyloidosis (CLA). CLA is seen in patients with the 634 mutation and occasionally in patients with an 804 mutation. The itchiness may be helped with topical steroid medications.

Hirschsprung's Disease

Hirschsprung's disease (HD) is also sometimes seen in MEN2A patients. HD is a disease of the large bowel that results in the bowel not moving as it is supposed to. This causes severe constipation and sometimes blockage of the bowel. HD can also cause nausea, vomiting, diarrhea, abdominal pain and distention, loss of appetite, slow growth, and in babies failure to thrive. Discuss any of these symptoms with your doctor and discuss HD and your specific RET mutation (usually seen in exon 10 mutations including 609, 611, 618, and 620). It is important to note that HD almost always first occurs in infancy, but in MEN2A patients it can show up later in life.

Papillary Thyroid Cancer

Some MEN2A patients develop papillary thyroid cancer with medullary thyroid cancer. So they have two types of thyroid cancer at once. Discuss with your doctor your RET mutation and risk of papillary thyroid cancer.

Genetics of MEN2A

MEN2A is caused by a RET mutation. RET stands for **RE**-arranged during **T**ransfection. You have 23 pairs of chromosomes. The RET mutation is located on chromosome 10. The RET gene contains genetic code for a receptor called a tyrosine kinase receptor and in MEN2A this receptor is always turned on. You can

imagine that for something that is supposed to be turned on only when needed, being turned on all the time results in problems (like MTC, PHEO, and hyperparathyroidism). For example, you turn on your blender only when you need it. You would never turn it on and leave it on. When a mutation causes something to be "turned-on" all the time, this is called a "gain of function" mutation.

So why is it important to know about your RET mutation? First, getting tested for a RET mutation via a blood test will confirm your diagnosis of MEN2A. More importantly, knowing your specific RET mutation will give you and your doctor lots of information to guide your monitoring and treatment. For example, if you have a 634 mutation, your MTC may be more aggressive than someone with a 609 mutation, so you will want to have surgery earlier and be monitored more closely afterward. Another example is a 631 mutation which is more likely to develop a PHEO than a 618 mutation. Lastly, once you know your specific mutation, your first-degree relatives can more easily be tested for MEN2A. This is because when the lab knows to look for one specific mutation (e.g. C609Y), they can test just for that and not waste time and money looking at all the possible RET mutations. **So the moral of the story is KNOW YOUR MUTATION because it matters!**

Often people ask when to get their kids tested. While this is a deeply personal matter with no perfect answer, knowing your mutation will help you decide. Some mutations have MTC show up as early as 6-months of age and in others MTC doesn't start to develop until puberty. Knowing your mutation will inform your decision about how to best monitor your children. If you choose not to genetically test your children, have a detailed plan with their pediatrician about what blood tests will be checked (e.g. calcitonin, CEA, calcium, PTH, plasma metanephrines) and starting at what ages.

The other frequently asked question is whether or not you can have a negative genetic test for MEN2A and still have MEN2A. The answer is yes. If you have two of the three tumor types (MTC, PHEO, hyperparathyroidism), you have MEN2A. Not all disease causing RET mutations have been identified yet. The chances of this happening in MEN2A are small, but it is possible.

What if you have no family history? Sometimes neither parent has MEN2A, and you are the first mutation in your family. This happens more often in MEN1 and 2B, though. In MEN2A, you could be the first mutation but it is much more likely that it was passed down from one of your parents. Since MTC doesn't have any symptoms, some families have no "history" but older generations actually do have MEN2A. They just don't know it yet. This is why, if your parents are living, they will want to be tested for MEN2A. If you are the first person diagnosed in your family, all your first-degree relatives should get tested – your parents, your children, and your siblings.

Resources:

Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4490627/pdf/thy.2014.0335.pdf

www.thyca.org

Multiple Endocrine Neoplasia Type 2: An Overview
http://www.nature.com/gim/journal/v13/n9/full/gim2011127a.html

www.cancer.gov

www.nih.gov