ePathway
THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

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ISSUE #084

IN THIS ISSUE

INTERESTING FACTS

6000

The approximate number of new cases of gynaecological cancer estimated in Australia in 2018[1].

1000

Approximately how many women are diagnosed with a gynaecological cancer each year in New Zealand[2].

30%

The percentage of pheochromocytomas and

Welcome to the September issue of ePathway

E-Pathway is an e-magazine designed for anyone who is interested in their health and wellbeing, and the integral role pathology plays in the diagnosis, treatment and management of diseases.

This month, we discuss

- Remaining vigilant towards gynaecological cancers
- Pheochromocytoma and paraganglioma, two of the more uncommon causes of secondary hypertension
- Primary aldosteronism is common and treatable but under-diagnosed
- Muscular dystrophy, one of the most common forms of hereditary disease

Hypertension is another name for high blood pressure. It is a very common disorder in clinical practice that can lead to severe complications, including heart disease, stroke and even death. Primary hypertension is the term used when there is no identifiable cause for the development of hypertension; secondary hypertension develops due to one of a variety of identifiable causes.

In this month's issue, we discuss endocrine causes of secondary hypertension, including pheochromocytoma and paraganglioma, which are rare, and primary aldosteronism, which is far more common.

This month, we also speak to Associate Professor Lyndal Anderson to discuss gynaecological cancers and the importance of remaining vigilant for subtle symptoms. We discuss these symptoms, risk factors and the important role of pathology in the diagnosis, treatment and management of all gynaecological cancers.

Muscular dystrophy is a group of inherited disorders that often cause progressive and irreversible muscle weakening and wasting. We spoke to Dr Belinda Chong to discuss the prevalence, symptoms and diagnosis of this hereditary disease.

Remember to follow us on Facebook (@TheRoyalCollegeofPathologistsofAustralasia), Twitter (@PathologyRCPA) or on Instagram (@the_rcpa). CEO, Dr Debra

paragangliomas with inherited origin[3]

Source:

[1] Australian Institute of Health and Welfare, 2018

[2] http://nzgcf.org.nz/facts-and-stats

[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3061287/

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Primary aldosteronism is common and treatable but under-diagnosed

We spoke to Dr Samuel Vasikaran, Department of Clinical Biochemistry, PathWest Fiona Stanley Hospital Network, Murdoch, about primary aldosteronism.

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Pheochromocytoma and paraganglioma: two of the more uncommon causes of hypertension

Endocrine hypertension is a secondary cause of hypertension involving hormone imbalance, most frequently involving the pituitary or adrenal gland. Endocrine causes of secondary hypertension include primary aldosteronism (the most common by far), Cushing's syndrome, pheochromocytoma, acromegaly, hyperparathyroidism, and hypo- and hyperthyroidism.

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Muscular dystrophy, one of the most common forms of hereditary disease

We spoke to Dr Belinda Chong, Head of Clinical Genomics at Victorian Clinical Genetics Services, Murdoch Children's Research Institute to discuss muscular dystrophy, a term which applies to a group of genetic diseases affecting the muscles that control movement.

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Remaining vigilant towards gynaecological cancers

We spoke to Associate Professor Lyndal Anderson, Senior Staff Specialist, Department of Tissue Pathology and Diagnostic Oncology at Royal Prince Alfred Hospital, to discuss gynaecological cancer.

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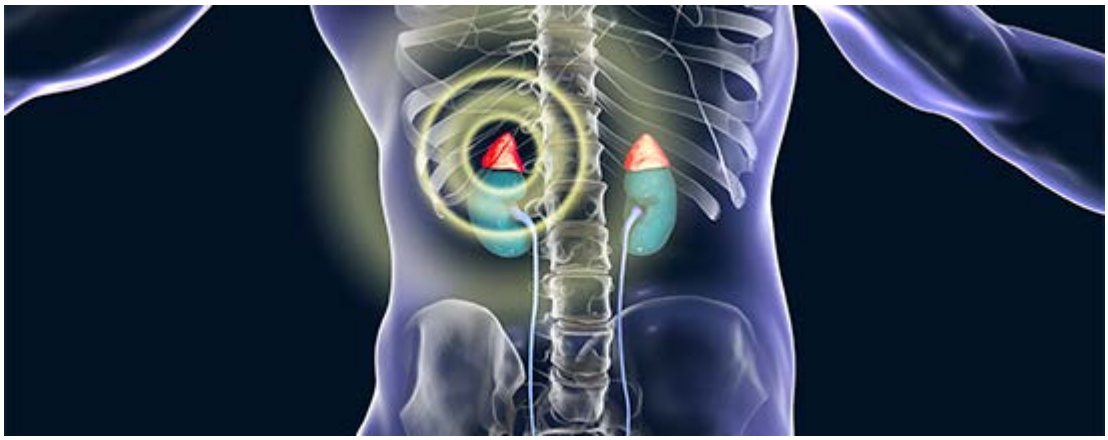
Primary aldosteronism is common and treatable but under-diagnosed



We spoke to Dr Samuel Vasikaran, Department of Clinical Biochemistry, PathWest Fiona Stanley Hospital Network, Murdoch, about primary aldosteronism.

Dr Vasikaran said,

“Primary aldosteronism is probably the most common cause of secondary hypertension (high blood pressure) in middle-aged adults. It is the autonomous excessive secretion of aldosterone, a hormone secreted by the adrenal gland. This hormone is important in maintaining blood pressure, along with electrolyte and fluid balance.

“Hypertension affects more than one-third of the population. The conventional wisdom was that primary aldosteronism accounted for less than 1% of hypertension, but about two decades ago, it was proposed that it actually accounted for up to 10% of patients with hypertension. Although this figure is still not universally accepted, primary aldosteronism is certainly far more common than previously thought. This is largely due to the fact that we are able to accurately diagnose a lot more cases than we previously could due to a new screening test.

This new test, proposed by Australian Endocrinologist Richard Gordon in the 90’s, was a paradigm shift in the diagnosis and management of primary aldosteronism. The test calculates the aldosterone-to-renin ratio in the blood. If the ratio is high then we suspect primary aldosteronism. Prior to this test, we measured aldosterone and renin but did not calculate the ratio, so we now identify a lot more cases.”

Primary aldosteronism has a number of causes. Approximately two-thirds of the cases

are due to bilateral adrenal hyperplasia (enlargement), in which both adrenal glands are producing an excess of aldosterone. Approximately one-third of cases are due to an aldosterone-producing adenoma – a tumour occurring on one adrenal gland that produces aldosterone excess. Rare causes include an inherited disorder called familial hyperaldosteronism which is caused by a genetic mutation.

“Not all patients with hypertension are screened for primary aldosteronism. Patients who are most at risk, or those that we recommend to be screened, would be those who have developed hypertension early in adulthood, those with a family history, and those with severe forms of hypertension and/or hypertension is hard to control. Another case for screening would be a patient with hypertension and low blood potassium levels, which is another indicator of primary aldosteronism. Of course if there is an adrenal tumour or an adrenal mass found, for example during a CT scan, then we would look for primary aldosteronism. Those particular patients would then be tested to see if it is a non-functioning mass or if it is secreting something.”

The diagnosis and treatment of primary aldosteronism is extremely important, as individuals who are affected are at a higher risk of developing heart disease and stroke. In addition, primary aldosteronism is treatable and is potentially curable in some cases [1].

“Primary aldosteronism is a condition where the pathologist plays a very prominent role. Screening for the condition by measuring the aldosterone-to-renin ratio is now universally recommended. However, this is only a screening test and is not diagnostic, so if the test is positive, we would then go on to do a confirmatory test. The easiest and most common test is a saline loading test in which the patient is given two litres of saline intravenously over four hours. If the aldosterone (after intravenous saline infusion) is suppressed then it is not primary aldosteronism and if the saline does not suppress the aldosterone then the condition is usually confirmed.

“In these cases, we then test to see if the patient will be amenable to surgery. You cannot remove both adrenal glands – if you remove both glands, you may cure the patient of aldosteronism but you would cause other problems as the adrenal gland is essential for life. So, in the one-third of cases where the hypersecretion is coming from only one gland then we would remove the offending gland. Usually there is a tumour in these cases, but not always, and of course there are non-secretory tumours. There are a significant number of cases where the mass you can see on CT scans may not be the one that is secreting the aldosterone excess; therefore it is important to confirm that it is definitely the one the aldosterone excess is being secreted from. This is where we would do adrenal vein sampling.”

Adrenal vein sampling involves catheterising and taking a blood sample from each of the patient’s right and the left adrenal veins and then measuring aldosterone and cortisol levels. This shows whether the aldosterone excess is coming from both adrenal glands or from only one gland. If the excessive aldosterone is coming from one side, the gland can be surgically removed, which potentially leads to the cure of hypertension. If aldosterone excess is being secreted from both adrenal glands then the treatment is medical therapy, using drugs such as mineralocorticoid receptor antagonists (e.g., spironolactone).

“Adrenal vein sampling was a reasonably difficult procedure in the past, with only about 60% being successful. However, now we have started doing cortisol measurement by a point-of-care test in the theatre where the cannulation is done. This has improved the success rate to over 90% of cases. We are still waiting for TGA approval on that point-of-care kit. We use it at our centre with special permission from TGA, and are hoping that approval will be available soon for routine use at all centres.”

[1] Yang J, et al. Is it time to screen all patients with hypertension for primary aldosteronism? Med J Aust 2018;209:57-59.

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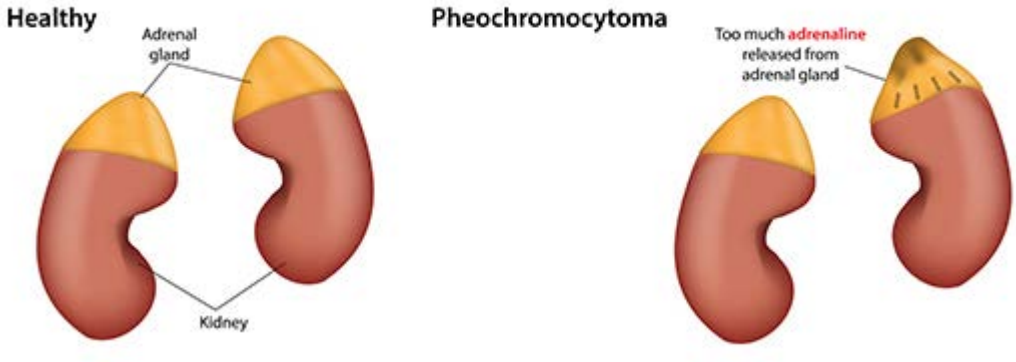
Pheochromocytoma and paraganglioma: two of the more uncommon causes of hypertension



Endocrine hypertension is a secondary cause of hypertension involving hormone imbalance, most frequently involving the pituitary or adrenal gland. Endocrine causes of secondary hypertension include primary aldosteronism (the most common by far), Cushing's syndrome, pheochromocytoma, acromegaly, hyperparathyroidism, and hypo- and hyperthyroidism [1].

In this issue, we spoke to Professor Anthony Gill, Professor of Surgical Pathology at Royal North Shore Hospital and The University of Sydney, about pheochromocytoma and paraganglioma, which are two of the more uncommon causes of hypertension.

Professor Gill discussed these rare tumours.

“Pheochromocytomas, and the closely related paragangliomas, are tumours of the glands which produce catecholamines (stress hormones, such as adrenaline). They are rare tumours, which occur in an estimated three people per million, per year, with paragangliomas being twice as common as pheochromocytoma.

“Pheochromocytomas arise in the adrenal gland, whilst paragangliomas develop in other parts of the body. The tumours can be separated into two categories: parasympathetic tumours, normally occurring in the head and neck and often asymptomatic; and sympathetic tumours which usually develop in the thorax, abdomen and pelvis.”

“Because pheochromocytomas produce stress hormones like adrenaline, patients may present with symptoms such as sweating, heart palpitations, panic attacks, high blood pressure or tremors. Some pheochromocytomas and paragangliomas do not secrete

stress hormones and patients are therefore asymptomatic."

Pheochromocytomas and paragangliomas probably account for 0.2-0.6% of hypertensive individuals. While most are 'sporadic' disease presenting in midlife, underlying genetic mutations are common and approximately 30% are hereditary [1].

"The role of the surgical (anatomical) pathologist at the biopsy, or when the tumour is removed, is to diagnose a pheochromocytoma and distinguish it from other tumours. Because pheochromocytomas are so rare, it takes a lot of training to be able to recognise this type of tumour.

If a patient is diagnosed with one of these tumours, the main treatment is surgery. Surgical resection cures 90% of pheochromocytomas and paragangliomas. However, it is important that the patient is given medication to control high blood pressure and other features of catecholamine excess before surgery. Otherwise patients can have a 'hypertensive crisis' during surgery which can be life-threatening.

"Pheochromocytomas and paragangliomas are probably the most strongly hereditary type of tumours and there are more than 20 different genes that cause these tumours to run in families. If the genes which cause these tumours are known to run in an individual's family, then the individual is able to undergo regular screening tests to identify any tumours, which can then be removed before any symptoms develop."

[1] Yang J, et al. Diagnosing endocrine hypertension: a practical approach. Nephrology (Carlton) 2017;22:663-677.

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Muscular dystrophy, one of the most common forms of hereditary disease

We spoke to Dr Belinda Chong, Head of Clinical Genomics at Victorian Clinical Genetics Services, Murdoch Children's Research Institute to discuss muscular dystrophy, a term which applies to a group of genetic diseases affecting the muscles that control movement.

Dr Chong explained,

"Muscular dystrophy is a group of inherited neuromuscular disorders that often cause progressive and irreversible muscle weakness and wasting. It is one of the most common forms of hereditary disease with more than 30 different types, each with a separate genetic cause."

Duchenne muscular dystrophy (DMD) is the most common type of muscular dystrophy and affects about one in 3,500 live male births. Given the way that it is inherited, DMD primarily affects boys. It is the most rapidly progressive of the childhood neuromuscular disorders. Becker muscular dystrophy (BMD) is less common, affecting between 1 in 18,000 and 1 in 30,000 male births. BMD's onset is usually in late childhood or adolescence, and the course is slower and less predictable than that of DMD.

Facioscapulohumeral muscular dystrophy (FSHD) affects the muscles of the face (facio-), around the shoulder blades (scapulo-), and in the upper arms (humeral). The signs and symptoms of FSHD usually appear in adolescence. However, the onset and severity of the condition varies widely. Milder cases may not become noticeable until later in life, whereas rare severe cases become apparent in early childhood. About 1 in 20,000 people are affected. Myotonic dystrophy is the most common adult form of muscular

dystrophy, affecting about 1 in 8,000 people worldwide.

“The first signs of muscular dystrophy can include delayed developmental milestones, for example problems with gross motor skills such as crawling and walking; learning and behavioural issues or difficulties with social interactions; frequent falling or poor balance; and elevated blood creatine kinase (CK), an enzyme found in the heart, brain, skeletal muscle, and other tissues. Increased amounts of CK are released into the blood when there is muscle damage, so high levels may indicate a problem with skeletal muscles.

“Prognosis varies according to the type of disorder. Some cases may be mild and progress very slowly over a normal lifespan, while others produce severe muscle weakness, functional disability and loss of the ability to walk”, said Dr Chong.

Each form of muscular dystrophy is caused by a genetic mutation, many of which are inherited. A large number of the genes causing the majority of cases have been identified, and their functions have been studied. Many of the associated genes are involved in providing strength to the muscle structure. For example, both DMD and BMD involve the DMD gene, and a deficiency of the protein dystrophin, produced by the DMD gene is known to cause muscle damage and progressive weakness.

“Individuals with a family history of muscular dystrophy are at higher risk of developing the disease or passing it on to their children. The majority of people with an affected child, though, have no family history of the condition. Although girls can be carriers and mildly affected by DMD, it's much more common in boys. However, female dystrophin carriers, while most often healthy, will require lifetime cardiac surveillance for cardiomyopathy, a disease of the heart muscle that prevents the heart from pumping blood around the body properly.”

The diagnosis of muscular dystrophy is based on a number of factors. If it is suspected that an individual has a medical disorder of their muscles, they will likely undergo a blood test to check the level of CK. If this level is elevated then genetic testing is the gold standard diagnostic tool and referral to a neurologist for evaluation is recommended.

“Clinical scientists and pathologists design and perform tests to diagnose, investigate and prevent muscular dystrophy. DNA testing is widely available for a majority of the conditions and is usually done from a blood sample.

“Medical research has led to a greater understanding of muscular dystrophy and potential new treatments are beginning to emerge however there is currently no cure. Medications and therapy can slow the course of the disease and several new treatments are now in clinical trial. For example, human trials of gene therapy relating to the dystrophin gene in DMD are currently taking place. However, it is still important to note that treatment for one type of muscular dystrophy may not necessarily help another type.”

Reference:
Muscular Dystrophy Australia (https://www.mda.org.au/disorders, accessed 19th September 2018)

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Remaining vigilant towards gynaecological cancers

We spoke to Associate Professor Lyndal Anderson, Senior Staff Specialist, Department of Tissue Pathology and Diagnostic Oncology at Royal Prince Alfred Hospital, to discuss gynaecological cancer.

"Gynaecological cancer refers to any malignancy arising in the female reproductive tract. This includes cancers of the uterus or womb, vulva, vagina, cervix, ovaries and fallopian tubes. It is estimated that over 6,000 new cases of gynaecological cancers will be diagnosed this year in Australia[1]. In New Zealand, approximately 1000 women are diagnosed each year[2]" said A/Prof Anderson.

“The symptoms of cancer of the ovary can be subtle. Altered bowel habit, bloating and loss of appetite may be noticed but can be easily dismissed by patients. Cancers of the uterus and cervix may be associated with bleeding after menopause or bleeding after intercourse. Patients should be very aware of new changes in their body, or new episodes of bleeding, and discuss them with their GP in the first instance.”

Although the causes of many gynaecological cancers are not fully understood, there are a number of risk factors to be aware of. General risk factors include increasing age, family history of cancer and various lifestyle factors such as smoking and increased body weight.

“Individuals who are most at risk of developing cancer of the uterus include those taking hormones (such as tamoxifen), those with diabetes and those who have never been pregnant. Risk factors for cancer of the cervix include exposure to high-risk human papillomavirus (HPV) and smoking. Ovarian cancer is associated with hereditary

syndromes such as BRCA1, BRCA2 and Lynch syndrome. The BRCA mutations are also associated with breast cancer, whilst Lynch syndrome is responsible for some cases of colon and bladder cancer for example. A family history of any cancer type, not necessarily of the reproductive tract, may be relevant," explained A/Prof Anderson.

Pathologists play an important role in the diagnosis, treatment and management of all gynaecological cancers. The information provided in the pathology report determines the critical patient treatment decisions that follow, and may help identify the risk to other family members such as sisters and daughters.

"Pathologists are responsible for the diagnosis of disease and for research into improving disease outcomes. This is achieved in many ways, including diagnosing changes on cervical smears, uterine curettings, biopsies from the cervix, vulva, vagina and fluid sampled from the belly (ascites), and by looking at whole organs such as the ovaries when removed surgically. Pathologists report on the type of disease and, for larger specimens, any hormone receptors the tumour may express and how far it has advanced.

"Different tumour types have vastly different prognoses; therefore it is imperative that the correct classification of a tumour is reported. The more extensive the disease, the harder it becomes to treat. It is estimated that nearly 2,000 women will die from gynaecological cancer in Australia by the end of 2018."

The chance of surviving five years after diagnosis of a gynaecological cancer is slowly improving, and now nearly 70% of women diagnosed with cancer will be expected to survive at least five years. The treatment for gynaecological cancers depends on a range of factors, including the type of cancer, its stage of development, its physical location and the patient's overall health.

"Surgery is a common method of treatment of established disease. Small lesions such as early cancers of the cervix can be treated with localised surgical procedures such as laser therapy. Ovarian cancers may require more extensive surgery. Chemotherapy and radiation therapy can be used for more advanced disease and also may assist with symptom control for some patients.

"If a patient has a strong family history of cancer then testing can be done to detect inherited mutations that increase the chances of developing cancer. If a high-risk mutation is confirmed in the patient, then risk-reducing surgery can be offered prior to cancer developing. For example, in carefully selected patients, ovaries can be removed prior to developing cancers.

"Exciting new treatment options, such as immunotherapy, will become available for the first time to Australian medical practitioners this year. Immunotherapy drugs, such as pembrolizumab, can be given in selected cases of uterine cancer, deficient in specific proteins as analysed by the pathologist, to assist the patient's own immune system to battle the tumour. This is expected to prolong survival in these patients."

Lifestyle factors should be modified where possible, for instance by stopping smoking and maintaining a healthy weight and diet. Early detection of disease is a major advantage for prolonged survival, and participation in screening programs such as the National Cervical Screening Program is essential. It is also important that women are vigilant to changes in their body.

"There are some great Australian websites providing more information, and your GP is always a great source of advice," concluded A/Prof Anderson.

See also:
https://gynaecological-cancer.canceraustralia.gov.au/

https://www.aihw.gov.au/

https://www.aihw.gov.au/reports/australias-health/australias-health-2018/contents/table-of-contents

[1] Australian Institute of Health and Welfare, 2018

[2] http://nzgcf.org.nz/facts-and-stats

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