ePathWay
THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

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- New nationwide research on genetic testing in Australia
- Seafood borne parasitic diseases - A single health approach is needed
- Diagnosing adrenal insufficiency

INTERESTING FACTS

660,000

genetic/genomic tests reported over the one-year genetics survey period (2016/17)

73

the percentage increase in molecular test requests over the past 5½ years

40

the number of major types of brain tumours[1]

22

Welcome to the March issue of ePathWay

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

This month's issue of ePathway looks at the following:

- Brain Awareness Week – Brain Cancer
- New nationwide research on genetic testing in Australia
- Seafood borne parasitic diseases - A single health approach is needed
- Diagnosing adrenal insufficiency

Brain Awareness Week took place from 16-22 March. This is a global campaign to increase public awareness of the progress and benefits of brain research. We spoke to Associate Professor Michael Buckland to get an insight into brain cancer and how pathology is absolutely pivotal to patient management.

The RCPA has unveiled new, nationwide research on Australia's medical genetic testing, which was conducted for the Department of Health. We spoke to Project Leads, Dr Anja Ravine (Genetic Pathologist) and Dr Sarah Nickerson (Genetic Pathology registrar) to discuss the findings.

Associate Professor Shokoofeh Shamsi discusses seafood-borne parasitic diseases with us. Doctor Shamsi was a speaker at the RCPA's recent annual conference, Pathology Update 2019. She explains that it's important for medical doctors to be aware that seafood-borne parasites exist, and for diagnostic tests to become available in Australia.

Finally, we approached chemical pathologist and endocrinologist, Associate Professor Damon Bell to discuss adrenal insufficiency, a disorder which occurs when the body does not produce enough adrenal/of a certain hormones. A/Prof Bell explains the important role of the pathologist in diagnosing adrenal insufficiency, which can have primary or secondary causes.

Remember to follow us on Facebook (@TheRoyalCollegeofPathologistsofAustralasia), Twitter (@PathologyRCPA) or on Instagram (@the_rcpa). CEO, Dr Debra Graves can be followed on Twitter too (@DebraJGraves).

the percentage five-year survival rate for brain cancer

Source:

[1] https://www.cancer.org.au/about-cancer/types-of-cancer/brain-cancer.html

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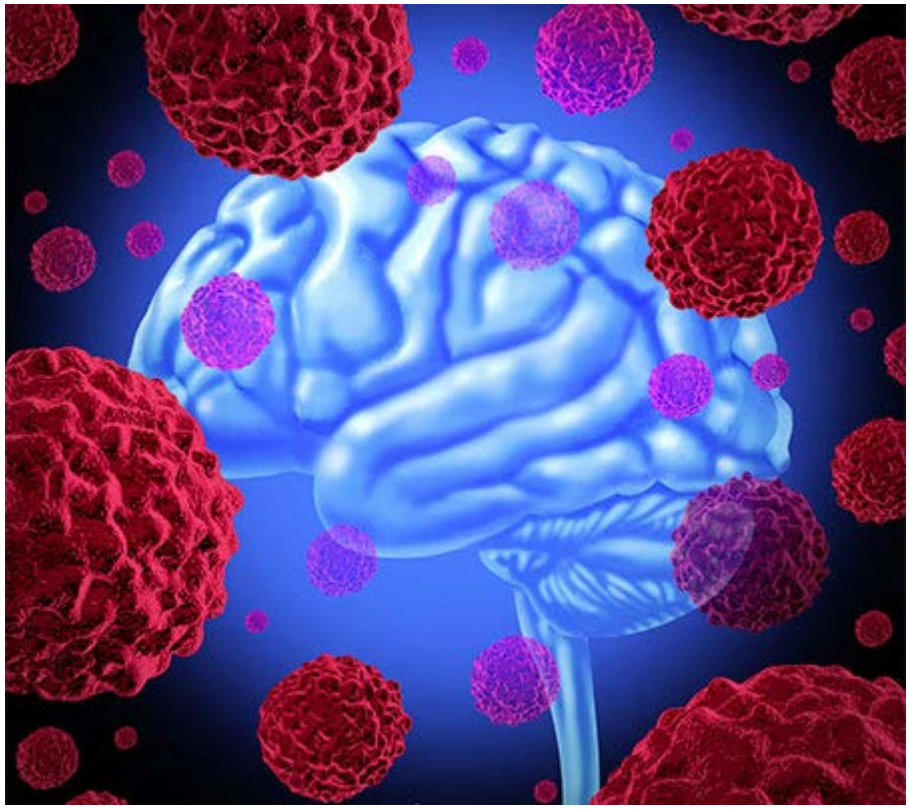

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findings. The data was reported at the RCPA's conference, Pathology Update, at the Melbourne Convention and Exhibition Centre.

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Seafood borne parasitic diseases - A single health approach is needed

We spoke with Charles Sturt University (CSU) Associate Professor Shokoofeh Shamsi, to discuss her new research[1] on seafood-borne parasitic diseases. Professor Shamsi was a speaker at the Royal College of Pathologists of Australasia's (RCPA) recent annual conference, 'Pathology Update 2019 – The Power of Personalised Pathology'.

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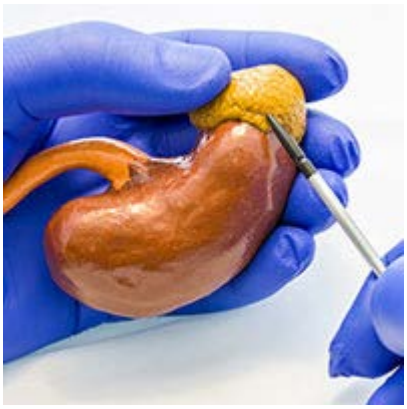
Diagnosing adrenal insufficiency

Adrenal insufficiency is a disorder where the adrenal glands do not produce enough of the hormone cortisol. We spoke to A/Prof Damon Bell, a Chemical Pathologist and Endocrinologist in Perth, Western Australia to discuss this condition.



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Brain Awareness Week

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“Brain cancer is the layman’s term for a malignant tumour which arises from the brain or its coverings. There are close to 2,000 cases per year in Australia, and the incidence is about the same in New Zealand, which is around 4-6 per 100,000 [1]. It is most common in men and is one of the highest cancer killers of children under the age of 15.

“There are around 40 major types of brain cancer. The main type is glioma; a tumour which arises from intrinsic brain cells called glial cells. Gliomas can be very different in onset, depending on the type. Gliomas in the older population tend to be aggressive, rapidly growing tumours, called glioblastomas, which have a median survival rate of around 16 months.”

The causes of brain cancer are not known. However, whilst the causes of brain cancer are uncertain, there are risk factors that have been established through research. These include: radiation exposure, age, male gender and genetic predisposition.

“What is really interesting is that we actually don’t know the causes of brain cancer. The main known risk factors are, exposure to ionising radiation, or a genetic predisposition to cancer. Our understanding of risk factors is about 30 years behind most of the other

common cancers. In addition, if you look at the survival rates of brain cancer over the last 30 years it is almost a flat line. In comparison, survival rates of breast cancer and other common cancers show a rise over time."

"There are a few common reasons why we are so far behind with brain cancers. One is that they are relatively rare. The other is that these tumours can be very aggressive and the survival rates are low, meaning there is not such a large vocal survivor group as there is with breast cancer or prostate cancer, where you see a lot of survivors 10 years on actively lobbying for funding. Brain cancer has been traditionally neglected in funding for scientific research."

The signs of brain cancer depend largely on where the tumour is located and its size. Some people present with a seizure, which could be the first sign. Other common presentations include difficulty seeing or blurry vision, headaches, and migraines. People may experience sensory changes or find they can't walk properly, which may occur over a period of days to weeks. Treatment for brain cancer can also vary according to the location of the tumour, including its size and type.

"The mainstay of treatment is surgery. The brain is different to a lot of other organs in the sense that it is very much location dependent on how aggressive that surgery can be. For example, if you have a tumour in a critical part of the brain, then surgery will not get the bulk of the tumour out. You could have a matchhead-sized tumour where your motor fibres are and you're hemiplegic. On the other hand, a patient could have a golf ball-sized tumour in the frontal lobe and barely notice it. Surgery would then be followed up with a standard chemotherapy and radiation therapy protocol.

"There have been very few new developments within brain cancer treatment and management. I think our understanding of the molecular biology of the brain cancers has been lagging behind a lot of the other cancers, but I think we are catching up rapidly. In the last 5-10 years we have seen an explosion of molecular data. In such a way that now the current WHO classification of brain tumours has actually had a radical makeover. Up until now, the classification has been done entirely on histology. Now for the first time the WHO has said that whilst we need histology, it is very important to include a layer of molecular information in order to provide a final integrated diagnosis.

"Gene changes are very important but they are important in the context of what you see. For example, a certain genetic change you see in one type of tumour might be fine, but if you see that genetic change in another tumour, that could be a really bad prognostic factor. It is this integrated diagnostics where layers of information are important.

"Pathology is pivotal to patient management. While MRI is enormously helpful, it cannot give the detailed diagnosis needed for accurate patient management. Tissue-based diagnosis is central and we are proud that, in our department, we are fortunate enough to be able to do everything. We can take a match head-sized biopsy, give a microscopic diagnosis, and from the same biopsy take all the genetic information we need in a relatively short timeframe to then issue an integrated diagnosis."

"The only way we are going to beat this disease is through more research, and pathologists have a central role in classifying, storing, and curating the tissue to enable scientists to perform research."

[1] https://brain-cancer.canceraustralia.gov.au/statistics

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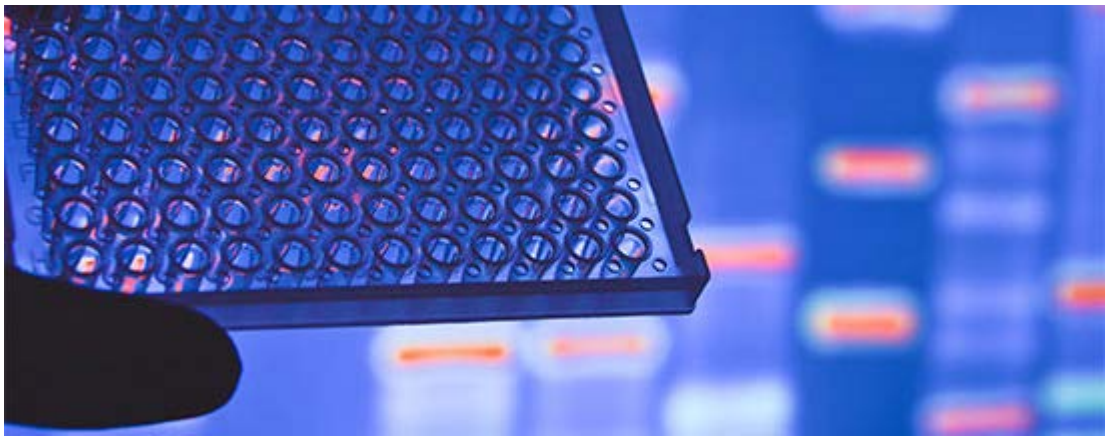
New nationwide research on genetic testing in Australia



The Royal College of Pathologists of Australasia (RCPA) has unveiled new, nationwide research on Australia's medical genetic testing, which was conducted for the Department of Health. We spoke to Project Leads, Dr Anja Ravine (Genetic Pathologist) and Dr Sarah Nickerson (Genetic Pathology registrar) to discuss the findings. The data was reported at the RCPA's conference, Pathology Update, at the Melbourne Convention and Exhibition Centre.

"The new findings reveal that genetic and genomic testing is becoming increasingly integrated into healthcare, reflected by a 73% increase in molecular test requests over the past 5½ years. The findings also show that test requests are made by a broad range of medical practitioners for a wide variety of clinical reasons. However, rapid advances in technology and genomic knowledge bring challenges. These challenges need to be addressed if genomic technology is to become further embedded within the healthcare setting" said Dr Ravine.

The RCPA undertook prior surveys of genetic testing in 2006 and 2011. "The Federal Government agreed that repeating the survey would provide a vital update on the nature and availability of genetic tests for Australian patients to make comparisons with historical data, provide information about workforce change requirements, and to facilitate modelling for future service provision" explained Dr Ravine.

All Australian laboratories known to have offered genetic or genomic tests for medical purposes during the 2016/17 financial year were invited to participate. "Although participation was voluntary, engagement was excellent with over 95% of laboratories

providing data" said Dr Nickerson.

More than 660,000 genetic/genomic tests were reported over the one-year survey period. The most common reasons for testing were for diagnostic purposes for constitutional (heritable) genetic conditions (55% of requests) or for cancer (12%). Other clinical indications included various forms of 'cascade testing' of relatives for familial gene variants; therapy selection; minimal residual disease (leukaemia) and transplant monitoring; population screening; several categories of prenatal testing, and preimplantation genetic screening. The stocktake also revealed that a further 308,000 newborn bloodspot screening tests, 147,000 maternal serum screening tests, and 67,000 biochemical genetic diagnostic tests were performed over the 2016/17 financial year.

The medical practitioners most frequently requesting genetic/genomic tests were General Practitioners and Obstetricians/Fertility/Fetal Medicine Specialists – together, these medical practitioner groups were responsible for half of all test requests. The remaining 50% of tests were requested by a wide variety of medical practitioners.

The survey revealed that a substantial proportion of genetic/genomic tests are now performed by the private sector. Thirty percent of participating laboratories were in the private sector and, together, they delivered almost two thirds of the total number of requested constitutional (heritable) and cancer (somatic) genetic tests. Just over half of the 83 responding laboratories were from the public sector; these laboratories performed approximately a third of constitutional and cancer genetic tests, but were responsible for a higher proportion of biochemical genetic tests (~60%). Of the other laboratories, 15% were research laboratories, delivering 0.2% of all tests; and 3.8% were Catholic/schedule 3, delivering 1.1% of tests.

Another important observation from the most recent survey is the growth in patient samples being transferred interstate or overseas for genetic/genomic testing. "The percentage of interstate transfers has more than doubled over the past 5½ years, to at least 20% of all genetic/genomic test requests", explained Dr Ravine. "A considerable proportion of laboratories did not provide details about the state/territory-of-origin of tested samples, which means that the overall rate of increase is likely to be even greater. The reported number of samples transferred to international laboratories has risen by 31% and, during the survey, it became apparent that large numbers of international test requests had bypassed the laboratories contributing to the stocktake, which means that this value is actually a considerable underestimate" said Dr Ravine.

These latest findings from the survey data revealed substantial changes to funding arrangements. For within-state tests, Federal funding (Medicare) covered almost half (49%) of the tests completed in 2016/17, compared with 35% in 2011. "The change in the proportion of tests covered by Federal funding was largely reflective of an increase in requests for tests with longstanding Medicare Benefit Schedule (MBS) item numbers, rather than resulting from the addition of new items to the MBS since the previous survey" explained Dr Nickerson.

For test requests referred interstate, Federal funding covered a higher proportion (approximately two thirds), with the vast majority of these being performed in the private sector. Most of the remaining tests that were transferred interstate in 2016/17 were paid for directly by patients. "Direct patient payments for genetic tests have doubled since the 2011 survey, and this is largely reflective of the growing uptake of non-invasive prenatal screening of maternal blood for common fetal chromosomal trisomies", said Dr Nickerson.

At the same time, findings from the survey reveal that the ongoing rapid advances in genomic technologies, particularly the advent of 'massively parallel' testing platforms and associated computing advances, are challenging many Australian laboratories. These testing platforms generate huge volumes of patient genetic data, necessitating secure and robust data storage solutions. A third of service laboratories considered their data storage facilities to be suboptimal for future demands.

"The big shifts going on within the industry have major implications for laboratory staffing", said Dr Ravine. "An example is the progressive upgrading of conventional

cytogenetic testing into more sensitive or efficient DNA-based methods. The net result has been a 40% fall in the volume of cytogenetic tests over the past 5½ years and a corresponding increase in newer molecular-based DNA tests."

"This means that there is a requirement for the workforce to upskill in order to effectively fully integrate these technologies into mainstream healthcare. A key matter requiring attention is ensuring future provision of both pathologists and medical scientists trained to the level required for safe provision of medical genomic tests to Australian patients. It is hoped that the findings from this research will further support the development of a National Genomics Policy Framework to improve coordination and consistency in approaches to integrating genomics in healthcare", explained Dr Ravine.

The survey yielded an insight into the contribution of Australian laboratories to global efforts to advance genetic knowledge and its clinical application. It is standard practice to compare patient genomic variations identified during clinical testing with variants recorded in a range of databases and within scientific literature. "Comparison with both local and international databases is an essential step in assessing the clinical significance of test findings for individual patients", explained Dr Nickerson. "Despite this heavy reliance on international variant databases, the findings reveal that most Australian genetic testing laboratories are yet to establish systems that enable them to contribute to this important international resource. Through sharing details of curated DNA variants, a broader repository of data is generated, which facilitates the accurate interpretation of genomic results and ultimately improves patient care."

All of the participating medical laboratories partook in this research on a voluntary basis. "We would like to acknowledge the superb contributions of each of the laboratories that participated in what was time-consuming data gathering. The survey provides representative data that can be used to describe current practices and trends in medical genetic testing in Australia", said Dr Ravine.

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Seafood borne parasitic diseases - A single health approach is needed

We spoke with Charles Sturt University (CSU) Associate Professor Shokoofeh Shamsi, to discuss her new research [1] on seafood-borne parasitic diseases. Professor Shamsi was a speaker at the Royal College of Pathologists of Australasia's (RCPA) recent annual conference, 'Pathology Update 2019 – The Power of Personalised Pathology'.

Professor Shamsi explained that it's important for medical doctors to be aware that seafood-borne parasites exist and for diagnostic tests to become available in Australia. She said that evidenced by literature, significant changes in parasitology teaching in Australian universities have adversely impacted the ability to detect, collect and identify these parasites in patients. Professor Shamsi said that seafood can contribute to a healthy diet and is safe when it is sourced, prepared and stored correctly, but there needs be more consumer awareness of best practices.

Professor Shamsi, who holds a Master's degree in Medical Parasitology and a PhD in Veterinary Parasitology, explains her passion for research into transmissible parasites between animals and humans and food safety. She has discovered more than 40 new parasite species and developed new protocols for detecting parasites in seafood. Professor Shamsi is a Senior Research Fellow at CSU and a member of the Graham Centre for Agricultural Innovation.

"Consumers are advised by many sources that seafood supports a healthy lifestyle, and rightly so. Not only is seafood recommended as a possible preventative measure against cardiovascular disease, but also for other conditions, such as Alzheimer's disease, diabetes or obesity. As a result, we are seeing more people consuming seafood, more

often. It's also becoming increasingly popular to eat raw, exotic or under cooked seafood. With this high demand for seafood comes the potential for diseases that have not previously been seen in humans. This could be due to our increased consumption of seafood or a combination of other factors, including climate change and other changes in our oceans," said Professor Shamsi.

"Although there are few reported cases of seafood-borne zoonosis in Australia, such as anisakidosis, this could be due to misdiagnosis. Other parasites that can affect patients are tapeworms, which can grow up to ten metres, and roundworms which can be problematic and can cause a mild, severe or even deadly allergic reaction. Crucially, there is currently no standardised diagnostic test in Australia for seafood-borne parasites. This means the patient needs to wait until their results come back from overseas, which can be very time consuming."

"We have recently seen cases where parasitic diseases found in fish (which have been reported in other parts of the world), actually presented differently in Australian patients, which is very interesting [3]. For example, in one case, in an Australian patient the parasite caused several weeks of vomiting and diarrhoea with increasing severity. The patient was unresponsive to medicine. Three weeks later she passed the worm alive through a bowel motion. In other parts of the world the parasite has been reported to penetrate the gastro-intestinal wall and eventually dies."

"We believe in and support research to show that seafood is a very healthy source of protein. We should remember that other food such as vegetables, red meat or poultry can also cause several severe diseases if they are not prepared properly or sourced from reliable places/resources. The difference is that we know and educate everyone about those diseases and we have several reliable diagnostic techniques for them in this country. When it comes to seafood-borne parasitic diseases, we need to bring all stakeholders onto the same page to make sure they are aware of the seafood parasites that can affect humans. The point is to make people understand that, like other food types, vegetables or red meat, seafood needs to go through certain levels of inspection and quality control before it is sold. It also needs to be cooked properly."

"As a result, investment is required in research and we need to have a national approach to/on the diseases caused by seafood-borne parasites, along with education to ensure a healthier community. We need educational campaigns to train all other parties involved with seafood and public health about these parasites. Ultimately, we want to be safe whilst still enjoying the benefits of one of the healthiest food sources known to humans," said Professor Shamsi.

Human infections with marine parasites are generally the result of ingesting uncooked seafood products. It is therefore important to ensure that, as with any other meat or vegetables, fish is cooked thoroughly before consumption or has been kept frozen if it is to be consumed raw. This simple and practical advice can make a big difference.

Literature suggests that some popular fish, sold in fish markets, may be infected with parasites transmissible to humans, however the number of reported human cases are low. Professor Shamsi believes that this low rate of human infection is due to a lack of expertise in Australia to accurately identify and diagnose seafood-borne parasitic infections.

"Recent Government risk assessments of the consumption of seafood have assessed the risk as low. But we believe the risk posed by seafood-borne parasites is underestimated. If you look at the history of human infection of seafood-borne parasites in Australia, you will see that between 1900 and 1950, a number of cases were reported. However, after 1950, there were no human cases published until 2011 [2] which were originally misdiagnosed or diagnosed overseas due to lack of expertise. We think this gap is partly because people working in this field retired or passed away and we lost their expertise. They were not replaced by anyone else and we believe this is partly responsible for the lack of information available on recent cases."

"University lecturers and educators teaching medical doctors, veterinarians and staff involved in the food industry, such as chefs, need to include a section on seafood safety, and in particular on seafood parasites and parasites of aquatic animals. At the moment if

you look at all the seafood safety guidelines that are taught in universities and other educational institutions, there is no or few mentions of seafood parasites," said Professor Shamsi.

The extent of the 'hidden cases' is unknown, partly due to this lack of education and subsequent misdiagnosis. Professor Shamsi advises establishing practical strategies to minimise the risk posed by these highly pathogenic, potentially deadly parasites.

"With all human cases of seafood parasites in Australia, they were ill after the consumption of raw seafood. It's important to know that if it's cooked properly, any parasites will be killed and they won't cause any risk to humans."

"Our research also suggests that the population of parasites in Australian waters has changed significantly during the last decade due to climate change and other factors. Understanding the extent of this change and its impact on our aquatic animals are other highly important areas that require research support."

References:

[1] Shamsi, S., Seafood-Borne Parasitic Diseases: A "One-Health" Approach Is Needed.Fishes, 2019. **4**(1): p. 9.

[2] Shamsi, S. and H. Sheorey, Seafood-borne parasitic diseases in Australia: are they rare or underdiagnosed? Internal Medicine Journal, 2018. **48**(5): p. 591-596.

[3] Shamsi, S., Seafood-borne parasitic diseases in Australia: how much do we know about them? Microbiology Australia, 2016. **37**(1): p. 27-29.

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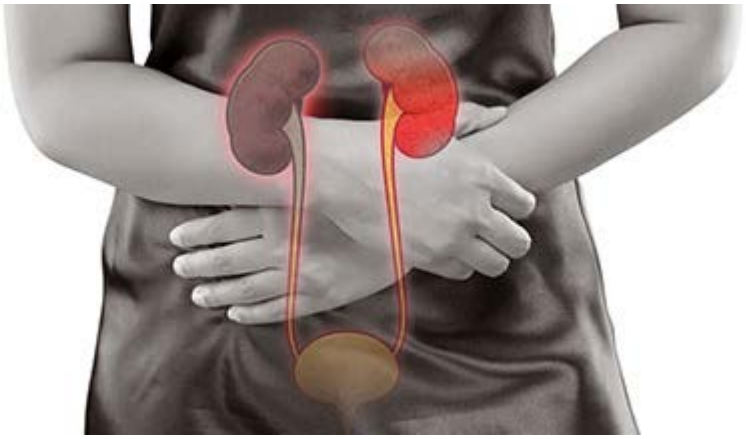
Diagnosing adrenal insufficiency



Adrenal insufficiency is a disorder where the adrenal glands do not produce enough of the hormone cortisol. We spoke to A/Prof Damon Bell, a Chemical Pathologist and Endocrinologist in Perth, Western Australia to discuss this condition.

“Cortisol is a glucocorticoid steroid hormone which is produced in the adrenal cortex and is vital for energy metabolism, blood volume and the body’s response to stress. Cortisol acts to increase the blood glucose level if it is low, and increases the metabolism of fats to ensure the body has adequate energy supplies. It works with aldosterone and other hormones to balance salts in the blood, which is crucial to maintain blood volume and blood pressure. In addition, cortisol coordinates the body’s anti-inflammatory response and prevents the release of pro-inflammatory substances.”

Cortisol has a diurnal rhythm, with a peak in the early morning with levels declining throughout the day to a trough overnight. Cortisol is produced in response to the release of adrenocorticotrophic hormone (ACTH) from the pituitary gland in the brain. Adrenal insufficiency has a prevalence of around one in 10,000 people in Australia and New Zealand.

“The signs and symptoms of adrenal insufficiency are usually non-specific and slow to develop. Occasionally a person may present in an adrenal crisis with severe shock and possibly a low glucose level. The symptoms of adrenal insufficiency include; lethargy, weight loss, dizziness, confusion, nausea and vomiting. Depending on the cause, people with adrenal insufficiency and high ACTH levels may develop patches of skin that are darker in colour than the surrounding skin, called hyperpigmentation.”

“The chemical pathology laboratory is key to the investigation of adrenal insufficiency.

The first step in investigating for adrenal insufficiency is to measure an early morning blood cortisol concentration, taken within two hours of normal waking time. If the cortisol is low, it is essential to ensure the patient has not had any steroid treatment (oral, IM/IV or inhaled) as this medication can suppress adrenal cortisol production by reducing ACTH stimulation. Patients on steroids do not usually need further investigation for adrenal insufficiency but, if they have been on long term therapy, they need to be slowly weaned off the steroids and may require review to ensure their adrenal glands are able to still produce cortisol once the steroid therapy is stopped."

Adrenal insufficiency is most commonly caused by autoimmune destruction of the adrenal cortex. It can also develop as a result of, or secondary to, destruction from tuberculosis, infiltrative conditions or metastatic malignancy.

"Once a low morning cortisol is confirmed, it is important to determine if the ACTH is high or low. A high ACTH with a low cortisol indicates adrenal disease, whereas a low ACTH and low cortisol indicates pituitary disease. The diagnosis of adrenal insufficiency is often not clear, and a short Synacthen test may be required. This involves measuring the patient's ability to produce cortisol after administering exogenous synthetic ACTH.

"The pathology laboratory is able to assist in determining if the adrenal insufficiency occurs as part of a polyglandular endocrinopathy, with multiple hormonal issues, or another inherited condition. This is done by measuring other hormone levels and performing genetic and immunological testing."

Adrenal insufficiency is very treatable once detected, with cortisol replacement available as oral tablets (cortate and hydrocortisone). Some patients also require the addition of fludrocortisone, a synthetic form of aldosterone.

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