ePathway
THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

DECEMBER 2018 | PUBLISHED BY RCPA

ISSUE #087

IN THIS ISSUE

INTERESTING FACTS

14,000

The number of Australians who will be diagnosed with melanoma this year.

1,800

The number of Australians who will die from melanoma this year.

75

The percentage of skin related deaths caused by melanoma, although it only represents approximately 2% of all skin cancers

Welcome to the December issue of ePathway

ePathway is an 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's issue of ePathway will look at the following:

- A reminder to be sun smart this summer
- Growth hormone deficiency, a cause for short stature in children
- Diagnosing and treating deep vein thrombosis and pulmonary embolism
- The importance of harmonising reference intervals

As Australia and New Zealand have the highest incidences of skin cancer in the world, we speak to world-leading melanoma pathologist, Professor Richard Scolyer, to discuss how to be sun smart this summer.

Dr Penelope Coates discusses growth hormone deficiency (GHD), how this can affect children's rate of growth and more, and how we investigate it.

We speak to Dr Prahlad Ho to discuss the risk factors, diagnosis and treatment of deep vein thrombosis and pulmonary embolism.

And finally, Associate Professor Graham Jones explains reference intervals, a common factor in reporting pathology laboratory results, and discusses the importance of harmonising reference intervals.

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).

Remember to be sun smart this summer

2,366

The number of cases of malignant melanoma reported in New Zealand in 2013.

356

The number of deaths in New Zealand caused by malignant melanoma

References:

http://www.melnet.org.nz/resources/melanoma-incidence-and-deaths-by-dhb

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LINKS

As we head into summer, it's important to remember the dangers of the sun, and to be aware of any changes in our skin. We spoke to world-leading melanoma pathologist Professor Richard Scolyer to discuss melanoma and non-melanoma skin cancer. Prof Scolyer is Co-Medical Director and Consultant Pathologist at Melanoma Institute Australia; Senior Staff Specialist, Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Sydney; and Clinical Professor, The University of Sydney.

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Growth hormone deficiency (GHD) can cause a slow rate or flattening of growth in children, and also changes in muscle mass, cholesterol levels, and bone strength in adults. We spoke to Dr Penelope Coates, Clinical Director of Chemical Pathology at SA Pathology, to discuss this condition, which affects around one in 4,000 to 10,000 children[1].

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"Australia and New Zealand have the highest incidences of skin cancer in the world. That is because we live in a place that basks under the sun. We're close to the equator and we have many people with pale skin which is not well-suited to this environment. We also have our "great Australian outdoor lifestyle" where we spend a lot of time outside. It is most of these things combined which makes us susceptible to getting skin cancer.

"We talk about melanoma the most because, although it represents only about 2% of skin cancers, it causes about 75% of skin cancer-related deaths. Around 14,000 Australians will be diagnosed with melanoma this year, and about 1,800 Australians will die from melanoma this year. Melanoma is the commonest cancer in Australians who are 15 to 39 years old, and the incidence in people over 60 is high and increasing.

"Non-melanoma skin cancer is also a major problem for our country. Although not as many people die from it as melanoma, it is four times more common than all other cancers combined, which is astounding. Basal cell carcinoma (BCC) is the most common of those; it's a tumour which causes local problems and rarely spreads beyond the site where it started. Squamous cell carcinoma is the other common type of non-melanoma skin cancer and unlike BCC, has more of a propensity to spread beyond the initial site, especially in people who are immunosuppressed for any reason."

The majority of skin cancers in Australia and New Zealand are caused by exposure to UV radiation in sunlight. Being sensible in the sun is a simple yet effective way to help reduce the risk of developing melanoma and non-melanoma skin cancers.

“There are five things that you need to do to protect yourself from the sun. First is to avoid sun exposure during hottest part of the day. Secondly, wear protective clothing when outside to protect your skin from the sun’s damage. Third, wear a broad brimmed hat. Fourth, ensure you wear sunglasses to protect your eyes, and finally, use a high SPF sunscreen which is SPF factor 30 or above. We actually also recommend that people apply sunscreen to their face every morning even when they are not spending time in the sun – it should be part of everyone’s routine.”

Early diagnosis of skin cancer is important and gives the best chance of successful treatment. Therefore, it is important to “know your own skin” to increase the chances of noticing any changes that may suggest a skin cancer, such as

- New moles,
- Moles that increases in size,
- An outline of a mole that becomes notched,
- A spot that changes colour from brown to black or is varied in colour,
- A spot that becomes raised or develops a lump within it,
- A mole with a surface that becomes rough, scaly or ulcerated,
- Moles that itch or tingle,
- Moles that bleed or weep,
- Spots that look different from the others.

“If you see any changes or anything different then seek medical attention. The really important message that we want people to heed is that if you detect melanoma early, then 90% of people will be cured by simple surgery – that’s why it’s really important to know the skin you’re in.”

“At Melanoma Institute Australia, we have also just launched an education program for high school students. People are generally well aware of the importance of sun smart behaviour in primary schools, and there is a ‘no hat no play’ initiative in effect in most of them. Teenagers are much harder to get the message through to, and so we recently launched a program aimed at educating high school students which we have named the Sun Smart Ambassador Program. High schools select students to become leaders who we then meet with and educate about the importance of sun safety. We provide them with presentation skills to go back to their school and educate their peers. We had a pilot in NSW in late 2018 and we’re going to roll it out across the country in 2019.”

Pathology is essential for the diagnosis of all skin cancers. If cancer is suspected, then following a skin biopsy a diagnosis will be made by a pathologist.

“Skin cancer can be suspected clinically but it is pathology that makes a definite diagnosis. Pathology is needed to diagnose all skin cancers. The pathological factors of the tumour also determine what it means for the patient in terms of risk of the disease spreading or recurring. The next phases of the management of skin cancer depend on what the pathologist recognises and reports.

“At Melanoma Institute Australia, our program spans prevention and management for those people at high risk of melanoma, early stage melanoma, and advanced melanoma. A lot of the major breakthroughs that have received publicity in recent years have been in relation to ways of treating advanced melanoma, particularly with immunotherapy. Up until less than a decade ago, once you had advanced melanoma your outlook was very poor – most patients would die within a short period of time - but now things are much better than that. The survival rates of people with advanced or Stage IV melanoma have more than tripled over the past ten years. Many people are having great responses and many people are being cured. But we still have a lot of work to do to reach our mission of zero deaths from melanoma.”

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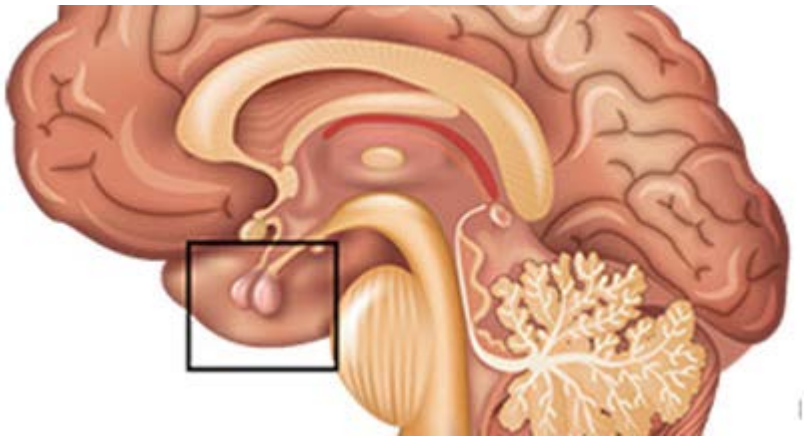
Growth hormone deficiency as a cause for short stature in children



Growth hormone deficiency (GHD) can cause a slow rate or flattening of growth in children, and also changes in muscle mass, cholesterol levels, and bone strength in adults. We spoke to Dr Penelope Coates, Clinical Director of Chemical Pathology at SA Pathology, to discuss this condition, which affects around one in 4,000 to 10,000 children. [1]

“Most importantly, growth hormone is essential for an increase in height in children; however, it is also responsible for other things such as muscle mass and even energy. Growth hormone is produced in a gland called the pituitary gland which is situated below the brain, just behind the bridge of the nose. A deficiency can develop if there is a problem with the pituitary gland, for example if there is a benign tumour in the gland. Failure of growth in children can also occur for other reasons, including nutritional problems, significant other illnesses, or even significant stress to a child. GHD can also be caused by a physical injury or through infections, but these causes are less likely.

“Signs of GHD all depend on the age at which it occurs. If a newborn baby has problems with the development of the pituitary gland, or has a benign tumour, then the sign might be low blood sugar. Therefore in a small baby, low blood sugar levels combined with anything ranging from difficulty feeding to even seizures, would suggest GHD. In older children, the obvious sign is failure to grow in height. Children are normally carefully monitored by their parents; growth charts are usually available in the handbook provided when you have a baby, so you should be able to see if your child is growing normally. These are the two most common signs,” said Dr Coates.

Growth hormone is secreted from the pituitary gland in a pulsatile manner, meaning in a burst-like or episodic way, rather than constantly. Therefore, as levels of growth hormone vary throughout the day, and peak and dip at different times, measuring the level of growth hormone at one single point in time does not always assist with the diagnosis.

“One of the least helpful tests is an isolated growth hormone test. If you see one single growth hormone level and it is well within the normal range for the age then that excludes a deficiency, but a low level doesn’t mean that the child has GHD, because of the pulsatile nature of the hormone. Typically, there will be some form of stimulation test which might be done by a paediatric endocrinologist; this is a specialist test which is typically done when it is suspected that you’re producing too little growth hormone.

“One of the most common stimulation tests employs a dose of arginine, an amino acid which is administered to the child to stimulate growth hormone production. Growth hormone levels would then be monitored by taking blood samples at timed intervals to monitor the effects. Exercise may also be done because growth hormone normally increases during exercise. There is a second hormone called insulin-like growth factor which is made in the liver in response to growth hormone and has levels which are much steadier during the day. In children, levels of both of these hormones are much higher than in adults; low levels of insulin-like growth factor could be suggestive of GHD, but that test is not the only thing that needs to be done.” said Dr Coates.

If the patient shows signs and symptoms of GHD and their growth hormone levels stay lower than they should during a stimulation test, then it is likely that there is GHD. Likewise, if GH levels do not increase when a person exercises vigorously, then they may have GHD and further testing would be required.

“One of the things that can confuse the issue is if the child is very overweight, as this can blunt the response to provocative tests. Typically, more than one test will be needed if people are going to think about treating a child with GHD.

“In addition, it is important to note that when we are interpreting a single level of growth hormone or insulin-like growth factor, then it needs to be compared to children of the same age. This is because there are two periods of very rapid growth: one in very early infancy, and one in teenage years during the teenage growth spurt. Therefore, it is very important to compare the child to an appropriate reference group, which is one of the things that the pathologist will do. The pathologist needs to have that information and have a good database of what normal results are at different ages,” said Dr Coates.

[1] http://www.childrenshospital.org/conditions-and-treatments/conditions/g/growth-hormone-deficiency

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Diagnosing and treating deep vein thrombosis and pulmonary embolism

We spoke to Dr Prahlad Ho, Director of Haematology at Northern Health, and inaugural Director of Northern Pathology Victoria, to discuss the risk factors, diagnosis and treatment of deep vein thrombosis and pulmonary embolism.

Deep vein thrombosis (DVT) is a blood clot that forms in a vein, typically in a leg. If not treated, it may dislodge and travel into the lungs. That process is called a pulmonary embolism (PE), which can be fatal. The most common provoking causes of DVT and PE include surgery, injuries and long-distance travel - typically greater than 4-6 hours.

Dr Ho said,

“DVT and PE affects about 1 per 1000 residents in Australia and is more common after injuries, surgery, pregnancy and hospitalisation, though there is a large variation in this. The common risk factors include male gender, age (over 65 years of age), and obesity.

“Another risk factor is thrombophilia, an inherited abnormality of blood coagulation that can increase the risk of thrombosis. Varieties of thrombophilia include Factor V Leiden mutation, prothrombin gene mutation, Protein C deficiency, Protein S deficiency and Anti-thrombin III deficiency. Some of these abnormalities, such as Factor V Leiden and prothrombin gene mutations, are quite common in the population and do not typically predict the risk of thrombosis in the general community. Careful consideration is therefore required for each individual, and it is important to discuss this with your doctor.

“Other risk factors include antiphospholipid syndrome, which can be acquired at any time of your life. In addition, cancer may also contribute to DVT and PE, and in certain

situations, we may test you for this. However, one-third of all DVT or PE cases occur with no apparent cause.”

DVT is normally characterised by pain and swelling in one leg, usually in the calf or thigh. Typically, the affected leg is significantly bigger and redder than the other leg. However, it is important to note that not all leg swelling is associated with DVT. If DVT is suspected, it is important that a diagnosis is made as quickly as possible, as the potential for the clot to cause a pulmonary embolism by travelling to the lungs is a major concern.

Pulmonary embolism is characterised by sharp chest pain and shortness of breath and can sometimes be difficult to differentiate from a heart attack. There is, however, a large spectrum of symptoms, and people with no visible symptoms might be diagnosed by low oxygen levels.

“Typically the diagnosis of DVT is through using a Doppler Ultrasound, which is a quick, painless way to check for problems with blood flow. Diagnosis of a PE is typically through CT scan. A blood test called a D-dimer, which measures the breakdown of clotting factors, can be also useful to predict the presence of a DVT or PE. This is sometimes used in some situations by your doctor, though the final diagnosis must be made using scans.”

“Pathology is crucial in the management of DVT and PE for a number of major reasons, including assisting with diagnosis; evaluating the underlying risk factors for the clot formation, including thrombophilia and antiphospholipid screen; as well as evaluating baseline bloods, particularly kidney and liver functions, to ensure the safety of using blood thinners. In patients using warfarin therapy, regular monitoring using a blood test called International Normalised Ratio (INR) is required every 1-4 weeks.

"The main treatment for DVT and PE is with anticoagulant medications – or 'blood thinners' – for a period of 3-6 months, although sometimes they may be prescribed long-term. There are two major groups of long-term blood thinners, these being the Direct Oral Anticoagulants (DOAC), and warfarin. The DOACs have been only recently available over the last five years and are more convenient than warfarin as they do not require regular blood tests. However, some conditions are not suited for the new DOAC therapy, in which case warfarin remains the preferred option. Certain types of anticoagulation injections may also be used for an inpatient.

“Other therapies in a small subpopulation of patients may include thrombolysis (“clot-busting agents”), or surgical intervention, such as endovascular procedures.” said Doctor Ho.

When taking blood thinners or clot-busting isn't possible or is not working well, your doctor may want to try a more involved procedure such as surgery, to insert a small filter in the vein or to remove a deep vein clot.

Measures can be taken to prevent DVT, including

- Avoiding sitting still and trying to move as much as possible, especially following surgery or during long-distance travel;
- Changes in lifestyle, including losing weight and quitting smoking;
- Regular exercise.

It is important that anyone experiencing symptoms of DVT contact their doctor. Immediate medical attention should be sought if any signs or symptoms of a pulmonary embolism are present, such as sudden shortness of breath; chest pain; feeling lightheaded or dizzy; rapid pulse; or coughing up blood.

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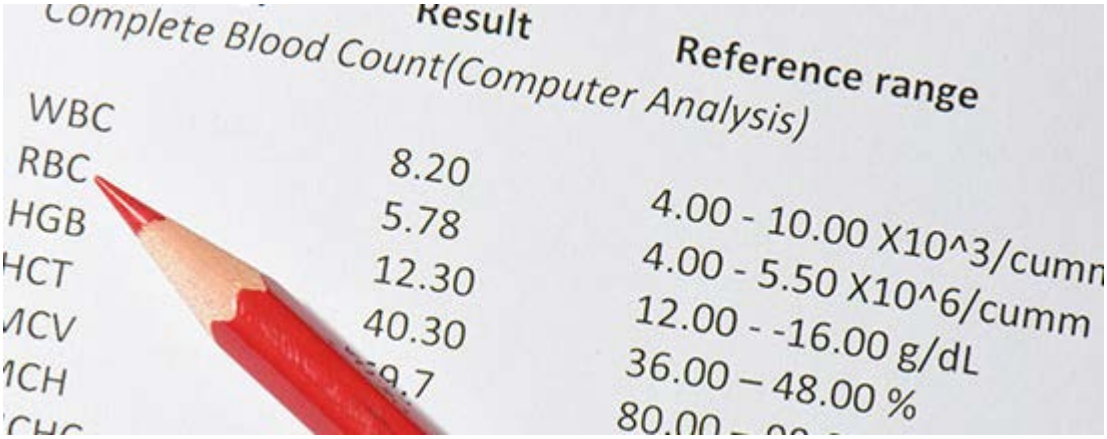
The importance of harmonising reference intervals



A reference interval (RI) is a common factor in reporting pathology laboratory results; it is used to transform a numerical value into clinically meaningful information. However, it is not commonly known that reference intervals can vary between laboratories, often meaning that similar numerical results can be interpreted differently in different laboratories. We spoke to Associate Professor Graham Jones, Chemical Pathologist at St Vincent's Hospital in Sydney, to discuss the importance of harmonising reference intervals.

"Reference intervals are a very commonly used tool to help with interpreting numerical pathology results. They allow the person looking at the report to see whether the value of a measurement, for example a serum sodium or a blood white cell count, is within the expected range for a healthy person.

"The result of a pathology test is only useful if you can compare it with something, and one of the things that it is most commonly compared with is what you can expect to find in a healthy person – that's what a reference interval tells you."

Reference intervals appear on nearly every report; however, different laboratories may interpret the same data differently. The interpretation of individual patient laboratory test results depends on the reference intervals with which they are compared. Harmonisation of this aspect of pathology testing is therefore now being undertaken around the world.

"It is the responsibility of individual laboratories to put the reference intervals on the report for each of the tests; however, because the laboratories do this themselves, then what you commonly find is that the reference intervals vary between different

laboratories. Harmonisation of reference intervals aims to remove any unneeded variation between laboratories, so we can be sure that the reports carry the same information for whoever is reading them.

“There are reasons that reference intervals should be different. For example, if a laboratory has a method which produces higher values than another lab's method, then the values in healthy people will be higher and the reference interval should be higher. Similarly, if the population is different, for example if the people in Melbourne have different kidney function than the people in Sydney, then those reference intervals should also be different. However, these variations can often be caused by complex things such as the statistics used, i.e. how laboratories have defined normality; where they have sourced their reference intervals from; or when those intervals were established. This variation makes the interpretation of results from different laboratories more difficult,” said Prof Jones.

Reading test results can be confusing for patients. With more people now having direct access to their pathology test results, especially with the introduction of My Health Record, the information needs to be clear. The reference interval against which the results are being compared is always included within the report, and it is important that patients only use the reference interval from the laboratory that performed the analysis, not from any other source.

“The importance of harmonising reference intervals is now recognised in many parts of the world. Australia has been leading the way in trying to address this issue and has now been joined by other countries, including Canada, the Netherlands and the UK.

“Reference intervals are not the only way that a laboratory test is interpreted. There will be other clinical decision points, for example, those used to diagnose diabetes, that might be assigned by expert bodies and international organisations. The medical literature and a doctor’s individual experience might also suggest what levels of a certain test might be found in a patient with a particular illness: for example, how high the creatinine is in someone that has kidney disease.”

The process of harmonising reference intervals is a huge undertaking, due to the complexity and the size and scope of the task. Australia has led the world in this important area of pathology testing, and the situation is now improving. Harmonised reference intervals have now been established for a number of commonly requested tests, and work continues to harmonise the reference intervals for more complex tests. [1]

[1] https://www.labtestsonline.org.au/news/pathology-update/harmonised-reference-intervals

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