VOL 20 2021 ISSUE 05 ISSN NUMBER 2313-8084

thesynapse

THE MEDICAL PROFESSIONALS' NETWORK

Imaging Prostate Cancer

Mismatch Repair Profiles in Oncology

Diabetic Painful Neuropathy

Covid-19 & Epilepsy

ENTRESTO®(sacubitril/valsartan)

Presentation: Each film-coated tablet of Entresto 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg contains sacubitril and valsartan respectively (as sacubitril valsartan sodium salt complex).

Indications: In adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Dosage & administration: The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient. In patients not currently taking an ACE inhibitor or an ARB, or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3 - 4 weeks) are recommended. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg, moderate or severe renal impairment (use with caution in severe renal impairment) and moderate hepatic impairment. Do not co-administer with an ACE inhibitor or an ARB. Do not start treatment for at least 36 hours after discontinuing ACE inhibitor therapy. Entresto may be administered with or without food. The tablets must be swallowed with a glass of water. Splitting or crushing of the tablets is not recommended.

Contraindications: Hypersensitivity to the active substances or to any of the excipients. Concomitant use with ACE inhibitors. Do not administer until 36 hours after discontinuing ACE inhibitor therapy. Known history of angioedema related to previous ACE inhibitor or ARB therapy. Hereditary or idiopathic angioedema. Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2). Severe hepatic impairment, biliary cirrhosis and cholestasis. Second and third trimester of pregnancy.

Warnings/Precautions: Dual blockade of the renin angiotensin-aldosterone system (RAAS): Combination with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan. Combination of Entresto with direct renin inhibitors such as aliskiren is not recommended. Entresto should not be co administered with another ARB containing medicinal product. Hypotension: Treatment should not be initiated unless SBP is ≥100 mmHg. Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported in patients treated with sacubitril/valsartan during clinical studies, especially in patients ≥65 years old, patients with renal disease and patients with low SBP (<112 mmHg). Blood pressure should be monitored routinely when initiating or during dose titration with sacubitril/valsartan. If hypotension occurs, temporary down-titration or discontinuation of sacubitril/valsartan is recommended. Impaired or worsening renal function: Limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73m^2). There is no experience in patients with end-stage renal disease and use of sacubitril/valsartan is not recommended. Use of sacubitril/valsartan may be associated with decreased renal function, and down-titration should be considered in these patients. Impaired renal function: Patients with mild-moderate renal function are more at risk of developing hypotension while patients with severe renal impairment may be at a greater risk of hypotension. sacubitril/valsartan is not recommended in patients with end-stage renal disease. Hyperkalaemia: Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists. If clinically significant hyperkalaemia occurs, consider adjustment of concomitant medicinal products or temporary down-titration or discontinuation . If serum potassium level is >5.4 mmol/l discontinuation should be considered. Angioedema: Angioedema has been reported with sacubitril/valsartan. If angioedema occurs, discontinue sacubitril/valsartan immediately and provide appropriate therapy and monitoring until complete and sustained resolution of signs and symptoms has occurred. It must not be re administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if Entresto is used in these patients. Black patients have an increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution is required and monitoring of renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised due to limited clinical experience in this population. Patients with hepatic impairment: There is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. Caution is therefore recommended in these patients. B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because it is a neprilysin substrate. Psychiatric disorders: Psychiatric events such as hallucinations, paranoia and sleep disorders, in context of psychotic events, have been associated with sacubitril/valsartan use. If a patient experiences such events, discontinuation of sacubitril/valsartan treatment should be considered.

Interactions: Contraindicated with ACE inhibitors, 36 hours washout is required. Use with aliskiren contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m^2). Should not be coadministered with another ARB. Use with caution when co-administering sacubitril/valsartan with statins or PDE5 inhibitors. No clinically relevant interaction was observed when simvastatin and sacubitril/valsartan were co-administered. Monitoring serum potassium is recommended if sacubitril/valsartan is co-administered with potassium-sparing diuretics or substances containing potassium (such as heparin). Monitoring renal function is recommended when initiating or modifying treatment in patients on sacubitril/valsartan who are taking NSAIDs concomitantly. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists including sacubitril/valsartan. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. Co-administration of sacubitril/valsartan and furosemide reduced C_{max} and AUC of furosemide by 50% and 28%, respectively, with reduced urinary excretion of sodium. Co-administration of nitroglycerin and sacubitril/valsartan was associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone, no dose adjustment is required. Co administration of sacubitril/valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, ciclosporin), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan. Appropriate care should be exercised. Co-administration of sacubitril/valsartan with metformin reduced both C_{max} and AUC of metformin by 23%. When initiating therapy with sacubitril/valsartan in patients receiving metformin, the clinical status of the patient should be evaluated.

Fertility, pregnancy and lactation: The use of sacubitril/valsartan is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. It is not known whether sacubitril/valsartan is excreted in human milk, but components were excreted in the milk of rats. Entresto is not recommended during breastfeeding. A decision should be made whether to abstain from breast feeding or to discontinue Entresto while breast feeding, taking into account the importance of sacubitril/valsartan to the mother.

Undesirable effects: *Very common (≥1/10):* Hyperkalaemia, hypotension, renal impairment. *Common (≥1/100 to <1/10):* Anaemia, hypokalaemia, hypoglycaemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhoea, nausea, gastritis, renal failure, acute renal failure, fatigue, asthenia. *Uncommon (≥1/1,000 to <1/100):* Hypersensitivity, postural dizziness, pruritis, rash, angioedema.

Packs sizes: Entresto 24 mg/26 mg – x28 tablets; Entresto 49 mg/51 mg – x28 tablets; Entresto 97 mg/103 mg - x28 & x56 tablets.

Legal classification: POM.

Marketing Authorisation Holder: Novartis Europharm Ltd, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

Marketing Authorisation Numbers: Entresto 24 mg/26 mg film coated tablets EU/1/15/1058/001; Entresto 49 mg/51 mg film coated tablets EU/1/15/1058/002-004; Entresto 97 mg/103 mg film coated tablets EU/1/15/1058/005-007.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing. Full Prescribing Information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872.

REFERENCES: 1. Maddox TM, Januzzi JL Jr, Allen LA, et al. 2021 update to the 2017 ACC Expert Consensus Decision Pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77(6):772–810. 2. Claggett B, Packer M, McMurray JJV, et al; for the PARADIGM-HF Investigators. Estimating the long-term treatment benefits of sacubitril–valsartan. N Engl J Med. 2015;373(23):2289-2290. 3. Lewis EF, Claggett BL, McMurray JJV, et al. Health-related quality of life outcomes in PARADIGM-HF. Circ Heart Fail. 2017;10(8):e003430. 4. ENTRESTO Summary of product characteristics. European Medicines Agency website. http://www.ema.europa.eu. Accessed June 2021.

2021-MT-ENT-19-MAY-2021

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Entresto®
sacubitril/valsartan

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TheSynapse

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Publisher:
Medical Portals Ltd
The Professional Services Centre
Guzi Cutajar Street, Dingli
Malta, Europe

Production: Outlook Coop

Printing: Europrint Ltd

OUR COLLABORATORS

The magazine is distributed free of charge to all Maltese doctors, pharmacists & dentists, as well as students of the aforementioned professions, with a print run of 3500 copies.

Annual subscription rates outside Malta: Six issues €100 or equivalent, worldwide

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TWO DOSES A YEAR[1*]

*LEQVIO is dosed initially, again at 3 months, and then once every 6 months.[1]

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†LDL-C reduction was maintained during each 6-month dosing interval.[1]

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LEQVIO®

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

PRESENTATION: Leqvio 284 mg solution for injection in pre filled syringe. Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml solution. Each ml contains inclisiran sodium equivalent to 189 mg inclisiran.

INDICATION: Leqvio is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

DOSAGE: The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months. ♦*Missed doses:* If a planned dose is missed by less than 3 months, inclisiran should be administered and dosing continued according to the patient's original schedule. If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months. ♦*Treatment transition from monoclonal antibody PCSK9 inhibitors:* Inclisiran can be administered immediately after the last dose of a monoclonal antibody PCSK9 inhibitor. To maintain LDL-C lowering it is recommended that inclisiran is administered within 2 weeks after the last dose of a monoclonal antibody PCSK9 inhibitor. ♦*Elderly, hepatic impairment, renal impairment:* no dose adjustment is necessary. Inclisiran should be used with caution in patients with hepatic and renal impairment.♦*Paediatric population:* The safety and efficacy of inclisiran in children aged less than 18 years have not yet been established. ♦*Method of administration*: Inclisiran is intended for administration by a healthcare professional via subcutaneous route. Each pre-filled syringe is for single use only.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

WARNINGS/ PRECAUTIONS: ♦*Haemodialysis*: The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after inclisiran dosing. ♦*Sodium content:* This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

INTERACTIONS: Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters. Therefore, inclisiran is not expected to have clinically significant interactions with other medicinal products. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

PREGNANCY, LACTATION AND FERTILITY: ♦There are no or limited amount of data from the use of inclisiran in pregnant women. As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy. ♦It is unknown whether inclisiran is excreted in human milk. A risk to newborns/ infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from inclisiran therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. ♦ No data on the effect of inclisiran on human fertility are available.

ADVERSE REACTIONS: *Common*: Adverse reactions at the injection site.

LEGAL CATEGORY: POM

PACK SIZE: One pre-filled syringe.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

MARKETING AUTHORISATION NUMBER: EU/1/20/1494/001

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc, Representative Office Malta, P.O. Box 4, Marsa MRS 1000 Malta. Tel +356 21222872.

2021-MT-LEQ-9-DEC-2020

References: 1. Novartis Europharm Ltd. Leqvio Summary of Product Characteristics.

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Sultans of Swing (& Waves)

Dire Straits were an exceptional British rock band active between 1977 and 1995. Their song, *Sultans of Swing,* originally released in 1978, is particularly close to my heart. The lyrics, written by frontman Mark Knopfler, were inspired by his presence in a pub in South London where a jazz band was performing; the name of the band was Sultans of Swing. Knopfler noted the contrast between the expectations tied to their name and the reality of an empty pub.

Maybe the reason why I am passionate about this song is that I am very sensitive to such dichotomous situations. Aren't we experiencing it in the manner in which the Covid-19 vaccine is distributed amongst countries? By the end of 2021 it is estimated that there would be 12.5 billion doses of vaccine which are enough to vaccinate the entire eligible population. Yet we see inequality all around us. Let us take Africa as an example. This continent trails behind, with only 10% of its population having received at least one dose. This goes beyond vaccine hesitancy but stems from the fact that Africa has little access to vaccines. The 10% vaccination rate is well below the WHO target of vaccinating 40% of the population of all countries by end-2021 and 70% by mid-2022. We are seeing this, even though it was apparent since Q2 of 2020 that the main challenge in the management of the pandemic waves would revolve around Africa. This mismanagement will inevitably lead to an African melting-point for different emerging variants which will then spill to the rest of the world, including Europe. We are literally shooting at each other's feet, in a concerted effort. And we seem to gloat at this.

Interestingly, according to Covax – a global effort co-led by Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI) and WHO to ensure equitable access to immunization throughout the world - around 100m of western countries' vaccines will expire in December and could easily go to waste. It is thus commendable that Malta has sent close to 500,000 Covid-19 vaccine doses to Rwanda, Ghana, Iran and Libya in the past few weeks; this compares extremely well to much bigger countries who pledges much but donated little. In keeping with the above, an important consideration of donations is that vaccines are being given to poor countries within three months of their expiry date. In such cases the expeditious transferring of delivery dates is the best way to mitigate this; at the time of going to print, Switzerland has become the first and only country so far to swap places in the vaccine supply queue with Covax, expediting the delivery of Covid vaccines to lower-income nations.

Sadly, such behavioural polarity is also seen at home. We personally show such traits, maybe inadvertently, when dealing with people, including patients. We also invariably see it ingrained in specific trade unions who present themselves as Archangels who blazon patient empowerment but then stand out in crippling the health department with countless directives. I ask, who suffers the brunt of these actions? I answer, it is the underprivileged and the marginalised. And yet ironically, against this backdrop, all of us trumpet the importance of mental health. And here again, I repeat the questions which I asked earlier this year … Who is to blame for the countless industrial actions spanning across the entire healthcare? The various healthcare professional sectors by any presumptuous demands? Or the government by its inherent inertia on specific issues? Can, however, the blame rest on specific union leader zealots?

I thus end this year's editorial with hope … that we truly discern what is good, what is important and what is crucial for us to survive harmoniously and truly live the Hippocratic oath … *help the sick and abstain from all intentional wrong-doing and harm* …

DR MURIEL BELLIZZI

Diabetic Painful Neuropathy

Managing the Advanced Disease

ABSTRACT

Diabetes is a complex chronic illness that can be associated with numerous complications. Amongst these is damage to the nervous system leading to different types of neuropathy. Pain can be a blessing in diabetic patients as painless neuropathy can lead to ulcerations. But on the other hand, having excessive pain can be debilitating by impacting the patients' quality of life. The high prevalence of neuropathy amongst diabetic patients warrants extreme care when undergoing the history and examination of such patients to rule out any diabetic peripheral neuropathic pain. When pain is present, it is essential to reduce it to improve the physical functioning, reduce psychological distress and ultimately improve the quality of life.

INTRODUCTION

Diabetes Mellitus (DM) represents a major health and economic burden as well as a global epidemic. In 2019, a worldwide estimate of 463 million adults between the age of 20 and 79 years of age suffered from diabetes. The *International Diabetes Federation* gave an estimated global prevalence rise to 10.4% by 2040 compared to 8.8% in 2015.[1] In 1981 a national WHO study held in Malta confirmed an exponential rise in diabetes in Malta. This was mainly attributed to the ageing population.[2] A higher prevalence of diabetes was also confirmed when compared to neighbouring countries.[3]

The commonest cause of neuropathy is diabetes.[4] Diabetic neuropathy is one of the complications that diabetic patients commonly suffer. It is a disabling and debilitating condition. The pathophysiology of this type of neuropathy is very complex and unclear but is thought to be mainly attributed to the microvascular injury to the vasa nervorum resulting in different types of diabetic neuropathy because of damage to the nervous system. The commonest type of neuropathy is the distal symmetric polyneuropathy. Also relatively common is injury to different fibres causing mononeuropathy multiplex, diabetic amyotrophy and autonomic neuropathy.[5]

DIABETIC PERIPHERAL NEUROPATHIC PAIN (DPNP)

Approximately 30-50% of patients with diabetes will eventually develop neuropathy.[6] Of these, 2-21% will complain of painful neuropathy. DPNP is highly underreported by patients and under-treated by doctors. This pain is frequently accompanied by depression, anxiety, and sleep disorders. The risk factors for developing DPNP include type 2 diabetes mellitus, women and patients of south Asian origin.

HISTORY AND EXAMINATION

Diabetes UK's footcare pathway for diabetics suggests an annual review of the foot. During the review, one should enquire about any pain which may be present, and if present, investigated (table 1).[7]

ANNUAL FOOT REVIEW: (FOOT EXAMINATION WITH SHOES AND SOCKS REMOVED)
Test foot sensation using 10g monofilament or vibration
Palpate foot pulses
Inspect for any deformity
Inspect for significant callus
Check for signs of ulceration
Inspect footwear
Ask about any pain

Table 1: Annual foot review for patients suffering from DM.

DISTRIBUTION OF PERIPHERAL NEUROPATHY

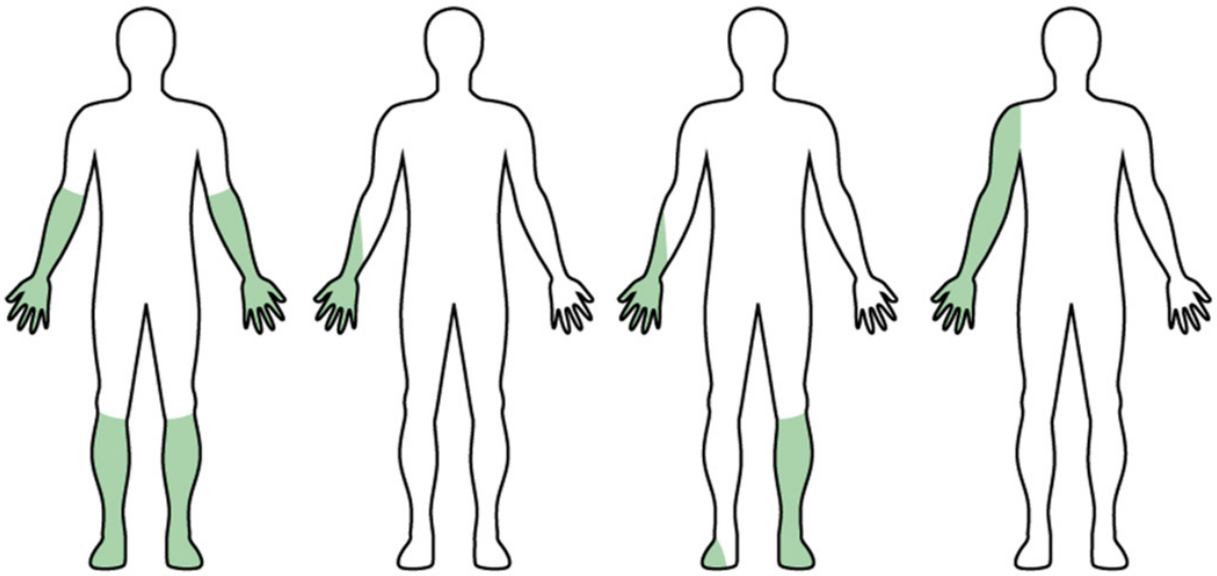


Figure 1: Distribution of pain

Pain varies in intensity, with most cases having moderate pain (numerical rating score (NRS) of 4-6), but around 30% of patients with diabetic neuropathy will suffer from severe pain (NRS 7-10). It is mostly described by patients as spontaneous burning pain in the peripheral limbs (see figure 1 for distribution of pain).[8]

KEY FINDINGS IN DISTAL SYMMETRICAL POLYNEUROPATHY INCLUDE THE FOLLOWING:

- Numbness, tingling pain or weakness*; stocking-and-glove distribution*.
- Patients with diabetic neuropathy are 2-3 times more likely to fall than those with diabetes and no neuropathy.
- Patients with severe neuropathy are at risk of ulcerations and lower-extremity amputations, with 15% developing an ulcer during the course of their disease.

TOOLS FOR DETECTION

The tools for detection of neuropathy are quite simple and cheap. These include the 10g monofilament test and the vibration perceptive test (figure 2). The *American Diabetes Association* (ADA) suggests the simple test in table 2 to identify any small or large-fibre neuropathy.[9]

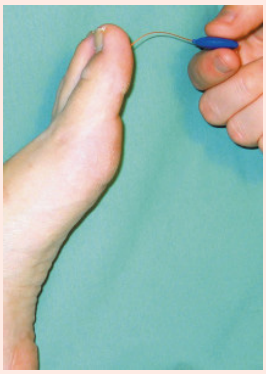
ADA -2019 NEUROPATHY ASSESSMENT TOOLS: THE FOLLOWING CLINICAL TESTS MAY BE USED TO ASSESS SMALL AND LARGE FIBRE FUNCTION AND PROTECTIVE SENSATION:

1. Small-fibre function: pinprick and temperature sensation
2. Large-fibre function: vibration perception and 10g monofilament
3. Protective sensation: 10g monofilament

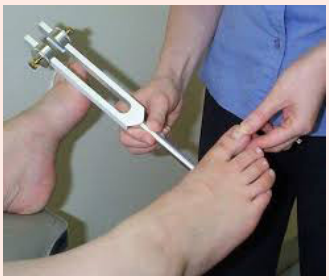
Table 2: Identification of small or large fibre neuropathy.

TARGETS OF MANAGEMENT OF DPNP

Neuropathy can be prevented with tight blood glucose control and strict screening with monofilament and tuning fork. Tight glycaemic control will help decrease the incidence but does not reverse the process. Once neuropathy is diagnosed, the only treatment available to these patients consists of improving glucose control and controlling the pain with various drug groups, the commonest being the anticonvulsants and antidepressants since the process is not reversible. The use of opioids as analgesics in the long term should be avoided. This is especially important when co-prescribing opioids and gabapentinoids as the combination can increase the risk of opioid-related overdose and death.[10] Managing DPNP should also focus on the improvement in other aspects which might arise because of such neuropathy including sleep, mood, functional capacity, quality of life as well as the prevention of any progression of the neuropathy and foot ulceration.



10g Monofilament Test



Vibration Perception Test with 128Hz tuning fork

Figure 2: Tools for detection of neuropathy.

NICE CLINICAL GUIDE ON THE MANAGEMENT OF DPNP IN NON-SPECIALIST SETTING

1. For people with painful diabetic neuropathy:
   a. Offer oral duloxetine as first-line treatment
   b. If contraindicated, offer oral amitriptyline
2. For people with persistent painful diabetic neuropathy:
   a. If first-line treatment was with duloxetine, switch to amitriptyline, pregabalin or gabapentin , or combine with pregabalin or gabapentin
   b. If first-line treatment was with amitriptyline, switch to or combine with pregabalin or gabapentin

If satisfactory pain reduction is not achieved with second-line treatment refer the person to a specialist pain service

Table 3: Pharmacological management of DPNP.[11]

NICE guidelines suggest the use of duloxetine, amitriptyline, pregabalin and gabapentin as the drugs of choice in managing DPNP (table 3). If these are not satisfactory, the patient should be referred to the pain specialist. 50% pain improvement in DPNP trials on pregabalin and gabapentin have been registered in 47% of patients and up to 48% of patients with duloxetine. The reduction rate has not shown to be dose dependent for duloxetine, but it is for pregabalin (27% reduction with150mg vs. 47% reduction with 600mg) and gabapentin (15.9% reduction with 600mg vs. 47.6% reduction with doses 900mg-3600mg).[11] Limited data is available on amitriptyline.

Other medications such as topical capsaicin, lidocaine patches, botulinum toxin and isosorbide dinitrate spray are less effective in managing DPNP.[12-16]

WHAT CAN THE PAIN CLINIC AT MATER DEI HOSPITAL OFFER?

Pharmacotherapy is not the only option for these DPNP patients. Neuromodulation has been suggested as last resort when other therapies have failed. Neuromodulation is a technique used to stimulate the nervous system by means of implantable devices (figure 3). This procedure is commonly used for deep brain stimulation for essential tremor and Parkinson's disease, cochlear implants for deafness and vagal nerve stimulation for epilepsy. In chronic pain, the stimulation relates to the dorsal column in the spinal cord. A current is applied to the large diameter fibres in the dorsal spinal cord by means of two leads that enter the epidural space via an epidural needle and move towards the desired site; these are then attached to a battery similar to a pacemaker.[17] The exact mechanism is still unclear, but the

CLASS	MODE OF ACTION	DOSE	COMMONEST ADVERSE EFFECTS
TCAs (amitriptyline, nortriptyline)	Serotonin and noradrenaline reuptake inhibition, sodium channel block, NMDA receptor antagonist	25-150mg daily	Dry mouth, dizziness, constipation, weight gain, vision problems, sexual dysfuction, sedation, prolonged QT interval
SNRIs (duloxetine, venlafaxine)	Serotonin and noradrenaline reuptake inhibition	Duloxetine 60-120mg daily; Venlafaxine 150-225mg daily	Adverse effects can be more severe than gabapentinoids such as dizziness, fatigue, nausea and insomnia
Gabapentinoids (gabapentin, pregabalin)	Calcium-channel blockers, reducing the release of presynaptic transmitters	Gabapentin 1200-3600mg three times daily; pregabalin 300-600mg twice daily	Dizziness, increase risk of suicide, headache, sedation, weight gain

Table 4: Different classes of drugs used in DPNP

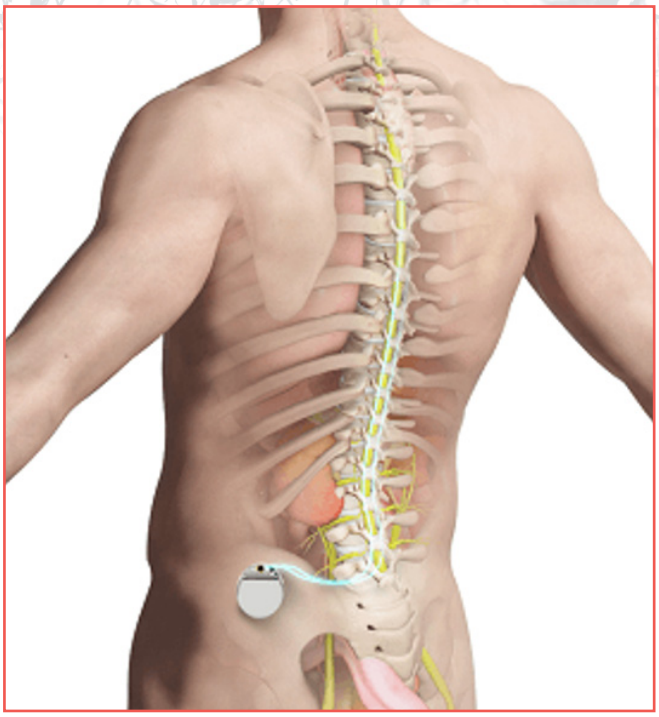


Figure 3: Neuromodulation performed at Mater Dei Hospital.[18]

most plausible explanations are the following two. First, by propagating the current up the brain and stimulating the periaqueductal grey it causes a descending inhibitory pathway initiation known as orthodromic stimulation i.e. in the direction of the fibres. The second postulation is that the downwards propagation, known as antidromic stimulation against the direct of current transmission, simulates the inhibitory neurones. These inhibitory neurones will ultimately cause dampening of the stimulation coming into the spinal cord. This reduces the extent of continuous stimulation from fibres in patients with PDNP, which ultimately causes less transmission of pain.

CONCLUSION

DPNP is common and is both underreported by patients and undertreated by doctors. As DPNP can negatively impact patients' quality of life, a bio-psychosocial approach to treatment is required. Prevention of neuropathy is possible if it is detected early. About half of the patients achieve a 50% improvement with current recommended treatments for DPNP. However, many patients remain poorly controlled due to inability to access adequate medication to control their pain or due to poor tolerance to the recommended medications. Referral to the pain clinic is recommended in patients with refractory pain.

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TAMARA ATTARD MALLIA & DR CHRISTIAN ZAMMIT

The Impact of COVID-19 on Epilepsy and its Management

ABSTRACT

The current coronavirus pandemic (COVID-19) has had a huge impact on our everyday life. This was even more so for certain cohorts of people, like those who suffer from epilepsy. Internationally, patients experienced difficulties in obtaining their anti-epileptic drugs and/or contacting their local pharmacy. Hospitals have been excessively burdened with COVID-19 patients leading to cancelled out-patients' appointments. Social isolation has increased epileptic injuries requiring emergency treatment. Epilepsy is not a risk factor to develop COVID-19, but the symptoms of one condition may indeed exacerbate those of the other. Remote healthcare by telemedicine provided a valuable means to mitigate the deleterious effect of COVID-19 on epileptic people.

1.0 INTRODUCTION

Epilepsy is a cerebral disorder characterized by recurrent seizures, the characteristics of which depend on the type phenomena and such patients may or may not experience loss of consciousness.[1] This condition is the second most common neurological disorder and is prevalent in approximately 0.7-4.6% of the general population and 6-8% of the pediatric population.[2] COVID-19, first identified in Wuhan City, China, over time got widely transmitted and became a worldwide pandemic.[3] COVID-19 has proved fatal in over 460 local cases and over 5.1 million people worldwide.[4] As a result, people had to socially isolate themselves and limit their contact with others so as to prevent further transmission. This left a significant impact on epileptic patients, among others, as their chronic condition could not be managed with the usual protocol.

1.1 ASSOCIATIONS BETWEEN COVID-19 AND EPILEPSY

Initial data obtained by the Center for Disease Control and Prevention (CDC) suggested that epilepsy is a risk factor for COVID-19, but further analysis by the CDC did not establish a direct link between these two conditions.[5,6] However, epilepsy possibly increases risks of more severe symptoms of COVID-19

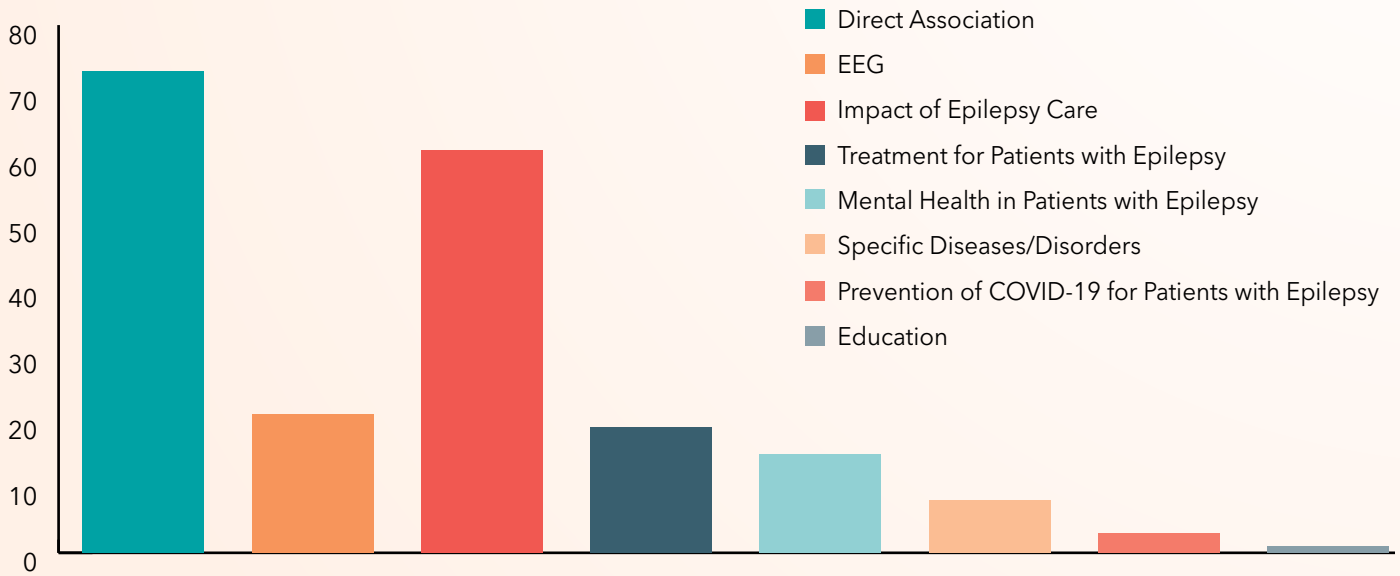

Figure 1: Articles correlating epilepsy and COVID-19 on PubMed[6]

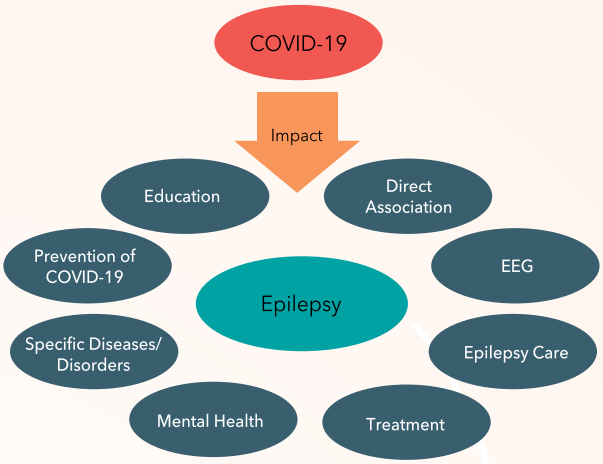

Figure 2: Epilepsy-associated factors that have been potentially impacted by COVID-19. These include education, EEG, mental health, and management among others.[6]

due to side-effects of anti-epileptic drugs (AEDs) that are mainly used to control seizures. AEDs namely, lamotigrine and phenytoin, suppress immunoglobulin levels, hence the patient is immunocompromised and at a higher risk of having complications with COVID-19.[7,8]

Epilepsy could nonetheless be due to, or associated with, other neurological conditions or congenital abnormalities that could have impaired immunity, rendering such patients susceptible to COVID-19 infections.[8] Additional research also hypothesized that COVID-19 may increase the risks of sudden unexpected death in epilepsy (SUDEP), since other viral infectious diseases like human herpes virus-6 (HHV6) seem to do so.[9,10] However, no such specific correlations with COVID-19 have yet been made.[5]

Literature on this subject is being regularly updated and as depicted in figure 1, there are already approximately 159 meaningful articles regarding epilepsy and COVID-19 associations on PubMed.

1.2 EFFECT OF COVID-19 INFECTIONS ON EPILEPTIC PATIENTS

As shown in figure 2, various aspects of epilepsy management were found to be significantly impacted by this pandemic. COVID-19 has been suggested to exacerbate seizure frequency and alter actions of AEDs.

Given that fever may trigger seizure onset, COVID-19 infection and its flu-like symptoms were suggested to exacerbate seizures in epileptic patients mainly due to the inflammatory reaction to the infection.[5,11]

Moreover, the coronavirus may enter the nervous system via angiotensin-converting enzyme receptor type 2 (ACE2) causing pro-inflammatory cytokines to enter the brain and be further produced by brain neurons namely, astrocytes and microglia. This potentially disrupts the blood brain barrier, increasing the levels of glutamate, gamma-amino butyric acid (GABA) and aspartate which induce seizures.[12]

A number of antiviral drugs used to treat COVID-positive patients (like remdesivir) have also been reported to interact with a number of commonly used AEDs (like carbamazepine).[13]

1.3 EFFECTS OF COVID-19 RESTRICTIONS ON EPILEPTIC PATIENTS

This pandemic has forced people to socially isolate themselves and maintain distance between each other. This has decreased rates of transmission but left serious challenges for everyone.

1.3.1 Prescription Availability

A survey conducted amongst people residing in the UK and suffering from epilepsy by Thorpe et al.14 found that around

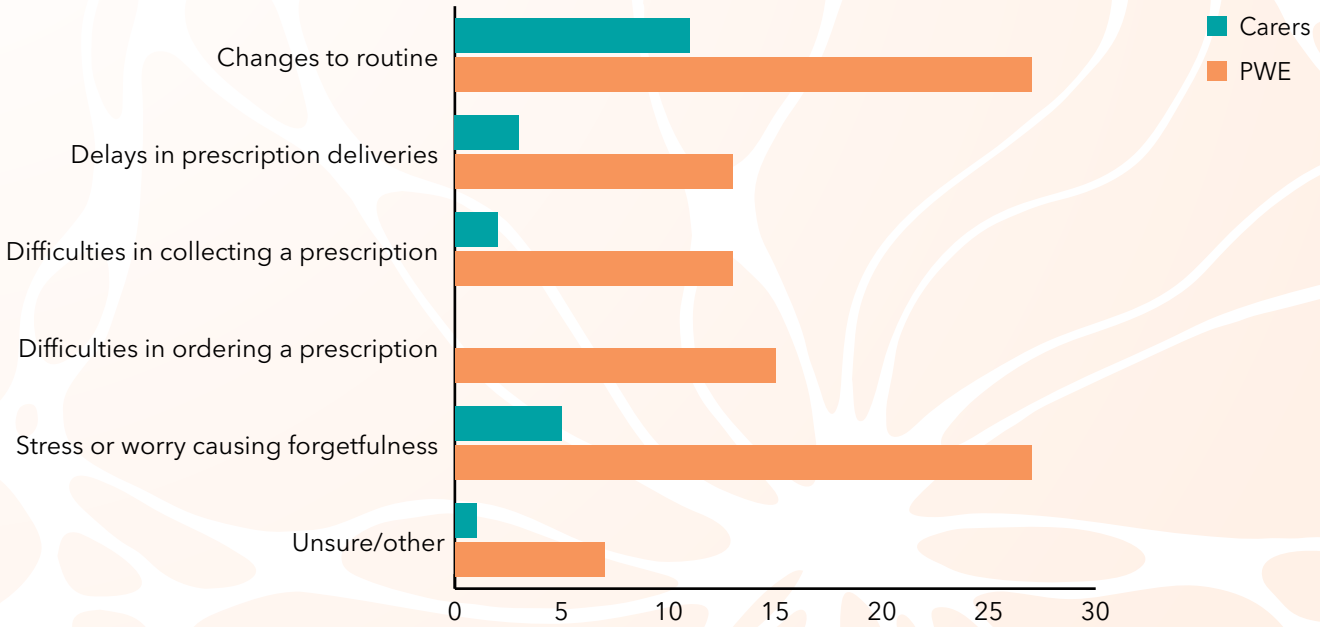

Figure 3: Mentioned reasons for not complying to AED regimen. Graph depicting reasons for not taking AEDs on time by care-givers [blue] and PWE [orange].[14]

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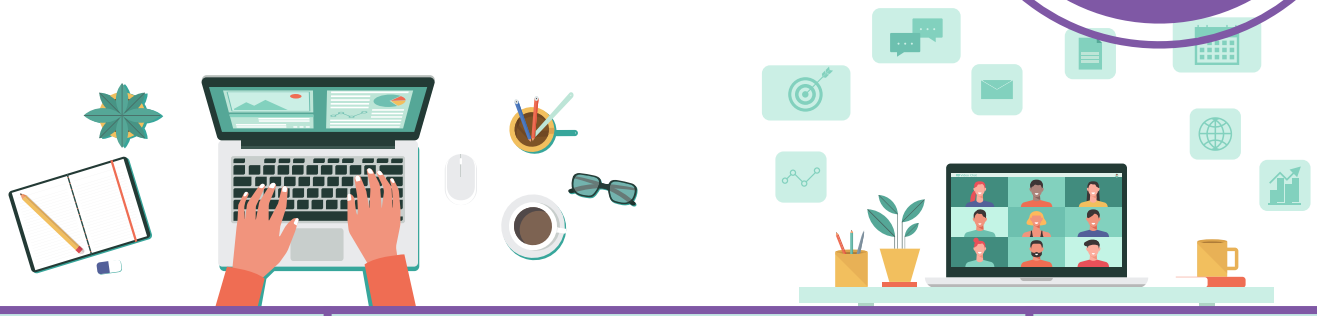

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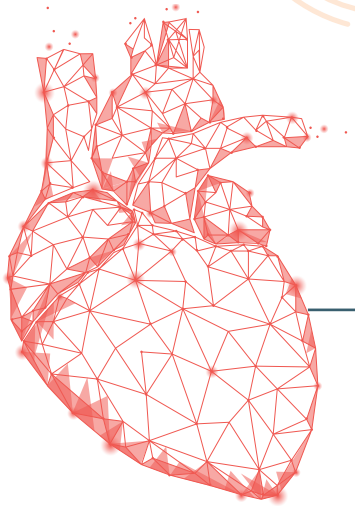

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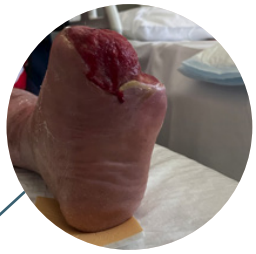

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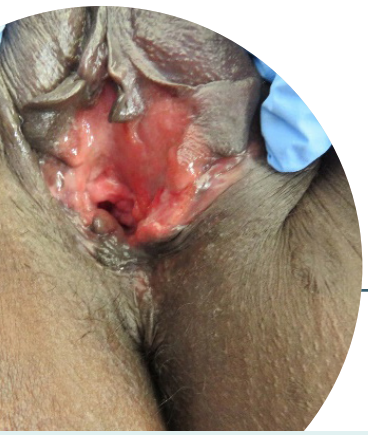

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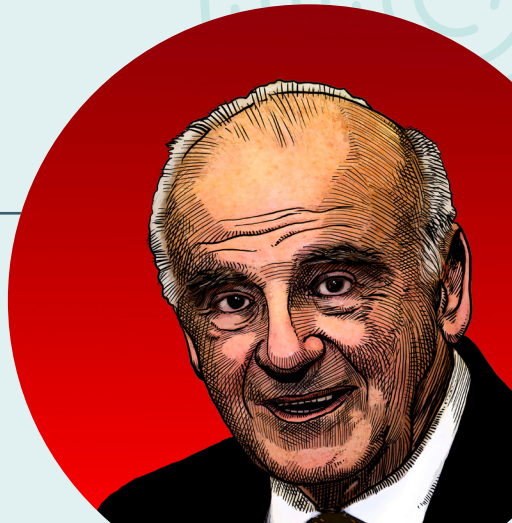

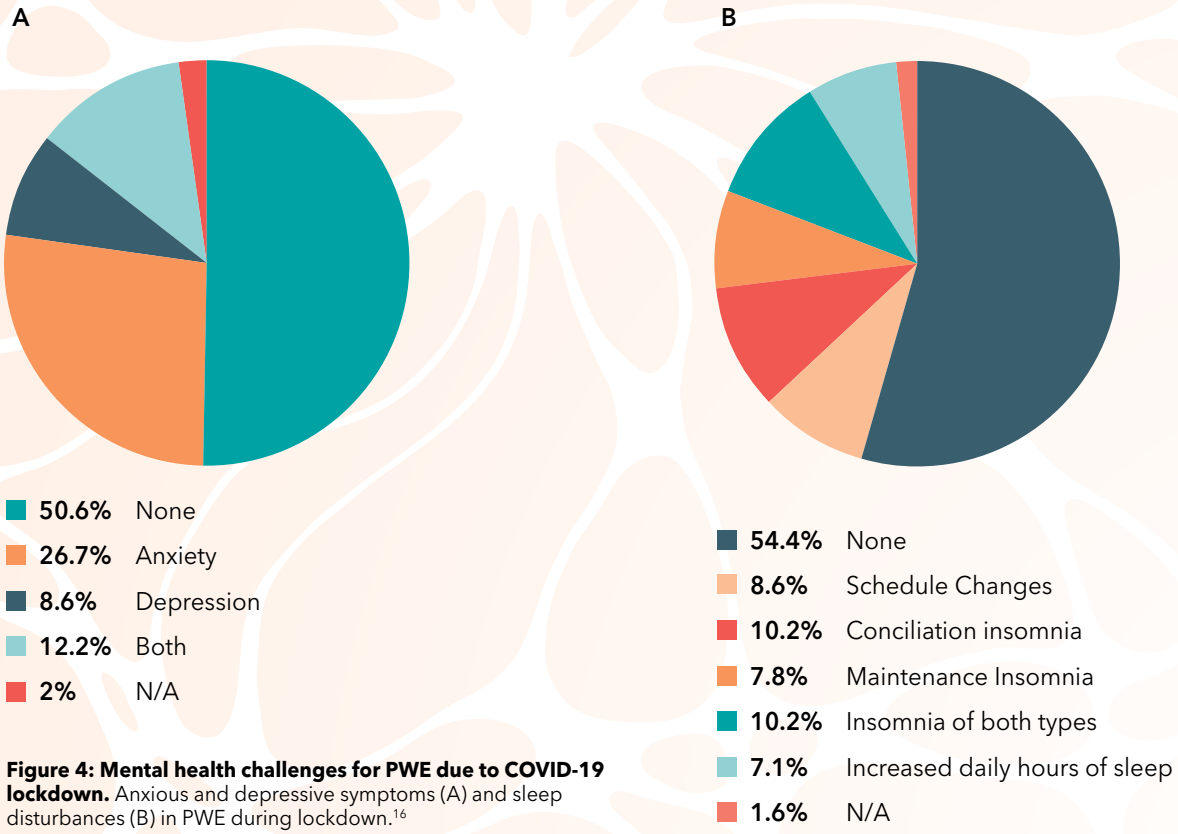

Figure 4: Mental health challenges for PWE due to COVID-19 lockdown. Anxious and depressive symptoms (A) and sleep disturbances (B) in PWE during lockdown.[16]

13% experienced difficulties in taking medication on time, mainly due to routine changes, and problems with acquiring a prescription (figure 3). Indicatively, this problem was more prevalent in people with epilepsy (PWE) rather than the caregivers.[15] Caregivers might have been too busy taking care of the family due to lockdowns; others also mentioned tele-working that kept them equally busy, as if they were working onsite. The authors also reported that contacting the physician or pharmacists proved difficult and PWE who had their dosage regimen changed during lockdown experienced prescription delays due to unprocessed treatment plans by their physician or pharmacy.[14]

1.3.2 First Aid and Emergency

In the study conducted by Thorpe et al.[14] approximately a quarter of the epileptic population was found to have lived socially isolated during the lockdowns; of which 23% made use of safety features namely, seizure alarms or emergency numbers linked with their physician. 15% of socially isolated patients had no one to provide them with first aid and approximately 38% of all PWE reported accidents that needed emergency help in 12 months. 41% of the latter group were living alone when the accident occurred. Indicatively, social isolation has increased the risks of injuries, especially during ictal episodes where patients may lose consciousness.[15]

1.3.3 Mental Health and Social Isolation

Lockdowns have left PWE isolated and often, helpless. Unfortunately, confinement-related anxiety and depression was significantly reported as shown in figure 4. Sleeping patterns were also significantly impacted due to changes in sleep schedules, longer sleeping hours and thought rumination.[16]

Such symptoms tend to reduce seizure control.[17] In fact, around 1 in 10 patients reported such changes in seizure control.[16] Moreover, recent evidence from southwest China showed psychological distress was at its peak at the time of the initial outbreak of COVID-19. The most prone were mainly drug-resistant epileptic patients as they suffered from more frequent seizures and in keeping with this, they spent longer periods searching for COVID-19 related information on the internet.[6,18]

Conversely, PWE that had employment-related changes (telework) which led to less work-related stress reported diminished seizure frequency.[16] Despite this being a minority, it is interesting that some forms of benefit in certain lifestyles were recorded. However, the negative impacts still seem to prevail and anxiety remained a bigger collateral effect to date.[19]

1.3.4 Access to Health Care

Many PWE have struggled with seizure control due to poor medical attention during the pandemic. Cancelled outpatient appointments have proved to be a major cause for concern as such patients may have required changes in their medication. Also, doctors were found to be deployed in COVID-19 wards, rendering them unable to see their patients.[20] Conversely, patients that where anxious of the hospital as being highly contagious, cancelled their

appointments. In fact, a study published in 2021 reported that 50% of patients with poor seizure control had not contacted their doctor.[20] In addition, most patients from the other half that decided toattend outpatients had poorly controlled seizures, indicating that hospital was kept as last resort. Notably, hospital appointments for patients experiencing a first seizure , with a view to make a clinical assessment , were also delayed in approximately 15% of cases.[16]

1.4 TELEMEDICINE AND VIRTUAL CLINICS

The use of technology to keep physically distant PWE connected with their doctors has been looked into before, but the pandemic provided the perfect opportunity to use this tool.[23,24] Telephone calls, instant messaging and SMSs enabled doctors to immediately help their patients despite their location. Video calls were particularly helpful since patients reported that seeing their doctor significantly decreased their anxiety symptoms. [16,25]

In keeping with the above, the pandemic has stimulated further epilepsy virtual clinics to be put up in various countries. Patients can still have their appointments from their own home or a digitally equipped place. Some centres in France also offer a remote, epilepsy follow-up device, so as to record the patients' EEG as well as other physiologic data; these are then electronically sent to the specialist. These clinics can also serve as potential distributors of AEDs whilst directly sending prescriptions of patients to pharmacies to keep the everything up-to-date.[26]

CONCLUSION

COVID-19 has left an indelible impact on the provision of healthcare around the world, and this includes the care received by PWE. This is a major cause for concern as doctors and patients have to think on their feet as to how they are to keep contact. Hence, technology and remote healthcare have proven formidable to prevent miscommunication, misdiagnoses or incompliance; decreasing complications and the need to seek urgent care is thus minimized. Proper epilepsy management and education to PWE's relatives is also crucial as the patient's household may become the first-responder when a seizure arises.

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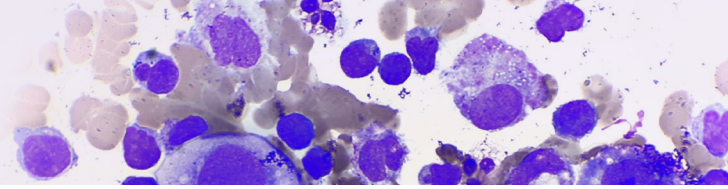

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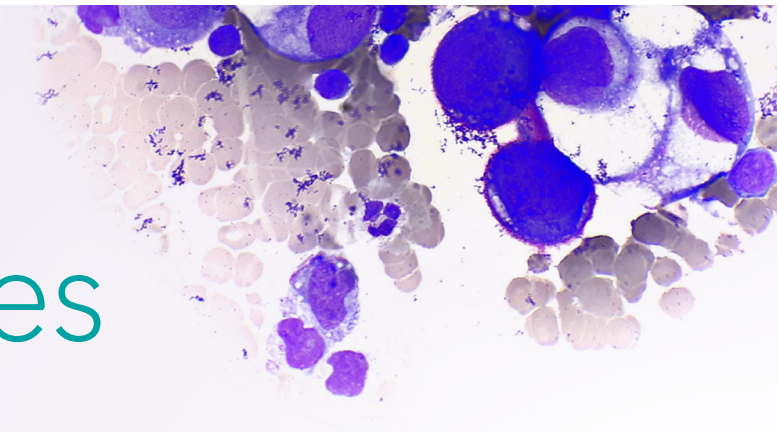

Mismatch Repair Profiles In Human Cancer

ABSTRACT

DNA mismatch repair (MMR) is a highly conserved biological pathway. Mismatch repair proteins excise and rectify DNA mismatches that result from the action of DNA polymerase during cell division. Commonly such DNA mismatches occur in microsatellites, which are repetitive DNA sequences in our genome. Thus, DNA MMR is decisively essential in maintaining DNA replication fidelity, avoiding the occurrence of mutations and giving stability to the genome. Clinically, MMR protein status is being increasingly used in the management of human cancer.

INTRODUCTION

History

Robin Holliday in 1964 proposed the notion that mismatched base pairs arise in cells and that such errors prompt their own repair during genetic recombination.[1] In 1975, Wildenberg and Meselson[2] showed that *E. coli* could correct DNA with mismatched nucleotides. Subsequently, Marinus[3] and Radmanet al.[4] did pivotal studies putting *E. coli* as a model for the MMR pathway. Their work demonstrated that the mutator genes MutS[5], MutL[6], MutH[7], UvrD[7] together with DNA adenine methylase[8], which were already recognized, were essential for the MMR process.

These works on the MMR pathway in *E. Coli* pioneered other extensive studies and today the pathway is well characterized. Briefly, the MMR process in *E. Coli* has the following main stages: (i) MutS binds to the mismatch, (ii) MutS recruits MutL and MutH, (iii) DNA strand containing the mismatched nucleotide is excised, and then (iv) the excision gap is resynthesized by the DNA polymerase.

Function

The main function of the MMR system is that it corrects mismatch nucleotides that are generated by the action of DNA polymerase during DNA replication.[9] Indeed, the MMR system increases the fidelity during replication by 100- to 1000-fold.[10,11]Besides preventing accumulation of mutations, MMR also plays in cell cycle checkpoint and apoptosis activation in the 'MMR-dependent DNA damage response'.[12]

LOSS OF MMR FUNCTION, MICROSATELLITE INSTABILITY (MSI) AND TUMORIGENESIS

Like practically all eukaryotic species, the human genome is full of tandemly repetitive DNA sequences. Microsatellites also called short tandem repeats (STRs) are typically repeated 5 to 50 times. The most commonly agreed number of nucleotides that define them is 1 to 6. Thus such repeats can be dinucleotide repeats, trinuleotide repeats, up to hexanucleotide repeats. During DNA replication in the S phase of the cell cycle, DNA polymerase tends to 'slip' (DNA polymerase slippage) in these repetitive sequences, causing mismatch of nucleotides, which are repaired by the MMR protein machinery coded by their respective genes, namely MSH2, MLH1, MSH6 and PMS2.

Cells that are 'MMR deficient' have what is called a 'mutator phenotype' with an increased tendency for spontaneous mutations.[13,14] These mutations can affect the whole genome but especially affect microsatellites. This creates 'microsatellite instability'(MSI) and favours tumorigenesis.[15,16]

The mutations are insertions or deletions. If these mutations affect microsatellites of coding genes they result in 'frameshift mutations' and result in the coding of 'truncated' proteins that have impaired function or no function at all.

The link between MMR deficiency and tumorigenesis has been extensively studied in Lynch syndrome, where autosomal dominant inherited (germline) mutations in the main MMR genes predispose to various cancer, mainly colorectal cancer (CRC, here called Hereditary Non Polyposis Colon Cancer,HNPCC) and endometrial cancer (EC).[17] In fact, 3% of all CRC and 2% of all EC are Lynch-syndrome associated.[17] Other cancers associated with Lynch syndrome include pancreatic ductal adenocarcinoma (PDAC),[18] gastric, esophageal[19] and upper urinary tract cancers.

TESTING FOR MMR AND MSI PROFILES

In clinical oncology, testing for MMR gene deficiency (MLH1, PMS2, MSH2 and MSH6) on tumour tissue is carried

out. The tests can include MMR immunohistochemistry (IHC) testing, PCR-based MSIanalysis, and DNA sequencing analysis. This is becoming crucial in order toguide treatment and predict prognosis. Always, test results are to be interpreted based also on clinical findings and family history.

MMR Immunohistochemistry Testing

MMR IHC staining of tumour tissue is done using the standard 'streptavidin–biotin–peroxidase' procedure. Here one is looking for MMR IHC antibodies, that mainly include those of MLH1, MSH2, MSH6 and PMS2. Tumour cells are scored as negative (MMR deficient) if they show total absence of nuclear staining, whilst adjacent tissue elements cells are scored as benign (MMR proficient) if they show nuclear staining.

PCR-based MSI Analysis

PCR-based MSI analysis is often done in combination with MMR IHC. The National Cancer Institute (NCI) recommends the following 'microsatellite marker panels', BAT-25 and BAT-26 (with mononucleotide repeats) and D5S346, D2S123 and D17S250 (with dinucleotide repeats).[20] Another useful kit contains five mononucleotide markers (BAT-25, BAT-26, NR-21, NR-24 and MONO-27). Xicola et al.[21]state that mononucleotide markers have a higher level of sensitivity and specificity in detecting the MSI-H phenotype.

Three phenotypes are defined:

1. Microsatellite Stable (MSS): none of the markers show instability
2. Microsatellite-Low (MSI-L): one of the markers show instability
3. Microsatellite-High (MSI-H): two or more of the markers show instability.

Phenotypes MSS and MSI-L are usually grouped as a single subset because rarely tumours with such phenotypes are MMR protein deficient.

Next Generation Sequencing

Next-generation sequencing (NGS) panels have been devised to detect mismatch repair deficient (MMR-D) and MSI-H based on mutational phenotype in various tumours.[22-25] Indeed, several panels and kits are available that allow high parallel sequencing of MMR genes. Moreover, NGS used for genome-wide analyses is possible and have shown that hypermutation (more than 10 somatic mutations per megabase) are more prevalent than previously thought, in adult cancer, reaching approximately 17% of cancers. This inflates the use of immunotherapy, since the latter is effective in cancers with an increased mutational burden.[24]

MMR AND MSI STATUS IN THERANOSTICS

Translational studies that analyse the history, genomics, epigenetics and pathology of MMR-D tumours are being used in theranostics, the latter being an emerging field of medicine that uniquely combines drugs and/or techniques to simultaneously or sequentially help in the diagnosis, prognosis and treatment of medical conditions, here cancer.

Diagnosis

Identifying patients who possibly have Lynch syndrome is essential as they and their family members need to be monitored. As already mentioned, Lynch syndrome is associated with various cancer types. Screening for MMR and MSI status in these associated cancer types can diagnose this syndrome. The molecular signature of Lynch syndrome is microsatellite instability from germline mutation in the DNA sequence that code for the MMR proteins. More commonly, tumours with MSI profiles are sporadic and are associated with epigenetic inactivation of the MMR genes.[26]

Prognosis

Currently there is valuable evidence supporting the use of the MMR and MSI status in the prognosis of colorectal tumours. However, less is known in extra-colonic tumours. Nevertheless, MMR status and MSI are being investigated worldwide in their use in the clinical prognosis for survival in many other tumours.

A case in point is that of PDAC. Specifically, patients who have PDAC that is MMR-D have a better prognosis and thus a better prolonged survival time.[27,28] In fact, Nakata et al.[27] report that patients with MSI-H PDAC have a survival time of 62 months, whilst those with MSI-L have 10 months.

In the MAGIC trial,[29] the consequence of MMR-D and MSI in curatively resected gastric cancer treated with peri-operative chemotherapy was evaluated. The trial showed that patients with MMR-D and MSI-H profiles had a better prognosis when treated with surgery alone, whilst those treated with chemotherapy peri-operatively had a differentially negative effect. The authors thus propose a prognostic stratification of patients based on their MSI and MMR profiles made on pre-operative biopsies.

Treatment

Immunotherapy is leading to a significant change in cancer treatment. Indeed, immunotherapy has spurred cancer research because it greatly improves the efficacy of treatment and overall survival in certain patients with various cancer types. Having said that, only a small proportion of patients respond to immunotherapy, and thus specific biomarkers need to be found to stratify those that are sensitive from those that are not. Currently, the key prognostic biomarkers for immunotherapy efficacy are 'Programmed Death-1' (PD-1) expression and defective mismatch repair genes, causing the MSI-H phenotype.

The MSI-H phenotype leads to an accumulation of somatic mutations in tumour cells causing a high mutational burden, increased expression of neoantigens and profuse tumour-infiltrating lymphocytes. All these changes are associated with increased response to immune

checkpoint inhibitors (ICIs). Thus, MSI status is emerging as a pivotal predictor of response to strategies based on immunotherapy. In keeping with this, the US Food and Drug Administrationfast-tracked the approval in 2014 for the use of ICIs for refractory MMR-D or MSI-H tumours, in both children and adults.

MSI status may also predict sensitivity or resistance of certain cancers to certain chemotherapies. For example, Pembrolizumab(PD-1 inhibitor) has been indicated for the treatment of unresectable or metastatic tumours that are MSI-H or MMR-D.

PDAC is a refractory cancer. Surgery is the only choice for the 15% to 20% of cases that are operable at diagnosis.[18] After surgery, the recurrence rate stands at 80% to 85%, and many patients after resection die to their disease.[30,31] A subset of PDAC patients are MMR-D and may benefit from a targeted approach using the FDA approved pembrolizumab.[32–35]

In a similar case scenario, this time involving colorectal cancers that are MSI-H or MMR-D, pembrolizumab can be prescribed if cancer has advanced after treatment with fluoropyrimidine, oxaliplatin, and irinotecan.[36]

More papers are coming out showing that MMR-D solid tumours respond to ICI.

CONCLUSION

The repercussions of MMR and MSI profiles in cancer continue to develop. It is becoming clear that these profiles are important in the diagnosis, prognosis and therapeutics of MSI-H cancers. MMR and MSI profile analyses are justified to screen for Lynch syndrome and also to stratify certain patients for their response to chemotherapy. More research across all cancer types will provide deeper understanding into MSI tumorigenesis and help further in developing better personalized therapeutic strategies.

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DR PIERRE VASSALLO

Imaging Prostate Cancer

Prostate cancer is the most common cancer in men.[1] It normally presents a long slow course with few or no symptoms. Consequently, in 17% of cases, metastatic disease is already present at the time of initial diagnosis. It shows great variability in its biological and clinical behaviour ranging from indolent localised disease to highly aggressive disease with metastases.

THE ROLE OF PROSTATE SPECIFIC ANTIGEN (PSA) TESTING

The screening test used for detecting prostate cancer is total serum prostate-specific antigen (PSA) measurement. Normal serum PSA levels increase with age. The standard normal total serum PSA level is 0.0-4.0ng/mL. However, the age specific ranges are as follows: 0-2.5ng/mL for age 40-49 years, 0-3.5ng/mL for age 50-59 years, 0-4.5ng/mL for age 60-69 years and 0-6.5ng/mL for age 70-79 years.

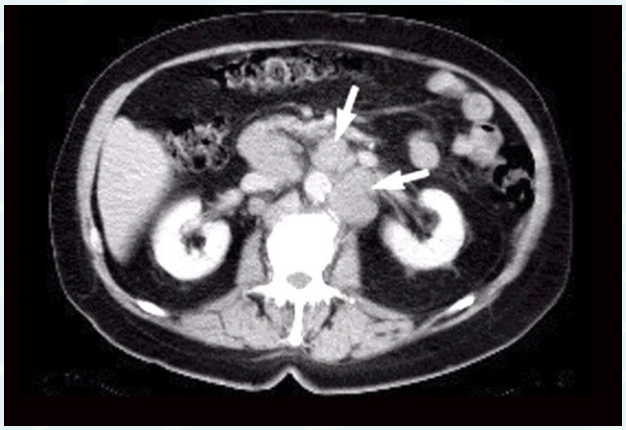


Fig 1. CT scan showing multiple enlarged retroperitoneal lymph nodes (arrows) due to spread of prostate cancer to the lymph nodes.

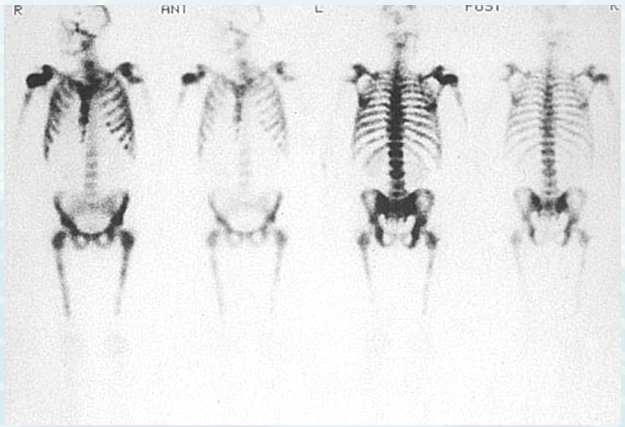


Fig 2. Tc-99m radionuclide bone scan showing marked radiotracer uptake in the spine, ribs, sternum pelvic bones and femora; this is known as a "superscan" appearance. Note that there is no renal excretion or soft tissue uptake of radiotracer due to avid uptake in bone.

Individuals with total serum PSA levels of 4-10ng/mL should be further investigated with a serum free PSA to total PSA ratio; free PSA levels >20% are indicative of benign prostatic disease, while levels <10% are more suggestive of prostatic malignancy. A total serum PSA level >10ng/mL is highly suggestive of prostate cancer with higher levels suggesting metastatic spread.

PSA is also monitored after definitive treatment for prostate cancer since a rising PSA level is usually indicative of recurrent prostate cancer. The PSA level should be measured every 6-12 months for 5 years and yearly thereafter.[2]

Shortly after radical prostatectomy, PSA levels should be undetectable (<0.1ng/mL). Persistently detectible PSA levels usually indicate residual viable tumour. PSA level recurrences occur in 20-35% of cases usually within 2-3 years after surgery.[3]

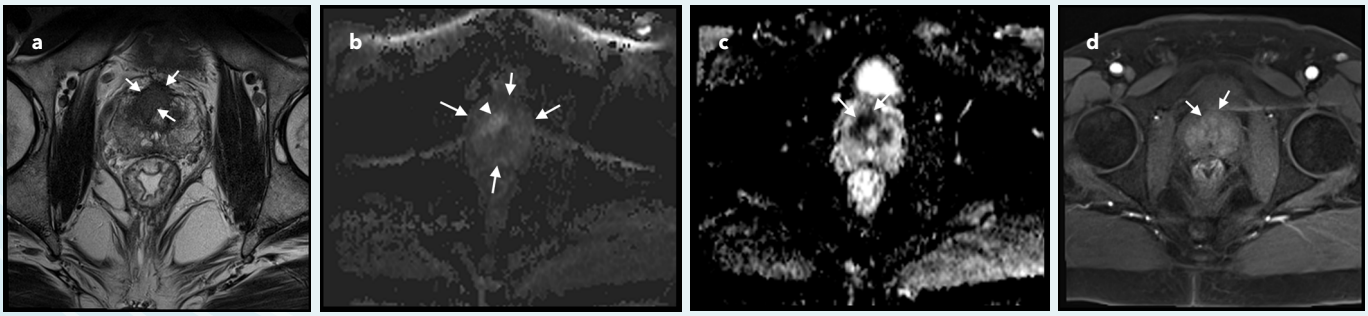


Fig 3. a. T2-w transverse image of the prostate showing an anterior (PI-Rads 5) tumour (arrows) as an area of low signal. b. Transverse DWI image showing the prostate (arrows) and the same tumour as in a that exhibits high signal. c. ADC map showing the same lesion as a dark area (arrows) confirming restricted diffusion. d. Transverse DCE image showing enhancement (arrows) that occurs contemporaneously with surrounding normal prostatic tissue (Case courtesy of Dr Matthew Bastian-Jordan, Radiopaedia.org, rID: 46481).

After radical prostatectomy, biochemical recurrence is defined as either two subsequent rises in PSA level after an initial undetectable post-prostatectomy PSA level, or two post-operative readings >0.2ng/mL.

After radiation therapy or tumour ablation, it is normal to have some residual PSA level even in cured patients. However, a rise of >= 0.2ng/mL above post-treatment levels is considered indicative of recurrence.

The median time for development of metastatic disease after biochemical recurrence is 8 years. Thus, the decision whether to treat or not and which form of treatment to implement will depend on the individual's health and life expectancy as well as prostate cancer-specific clinical, pathologic, radiologic, and genomic factors. Treatment will depend on whether disease is local, metastatic or both.

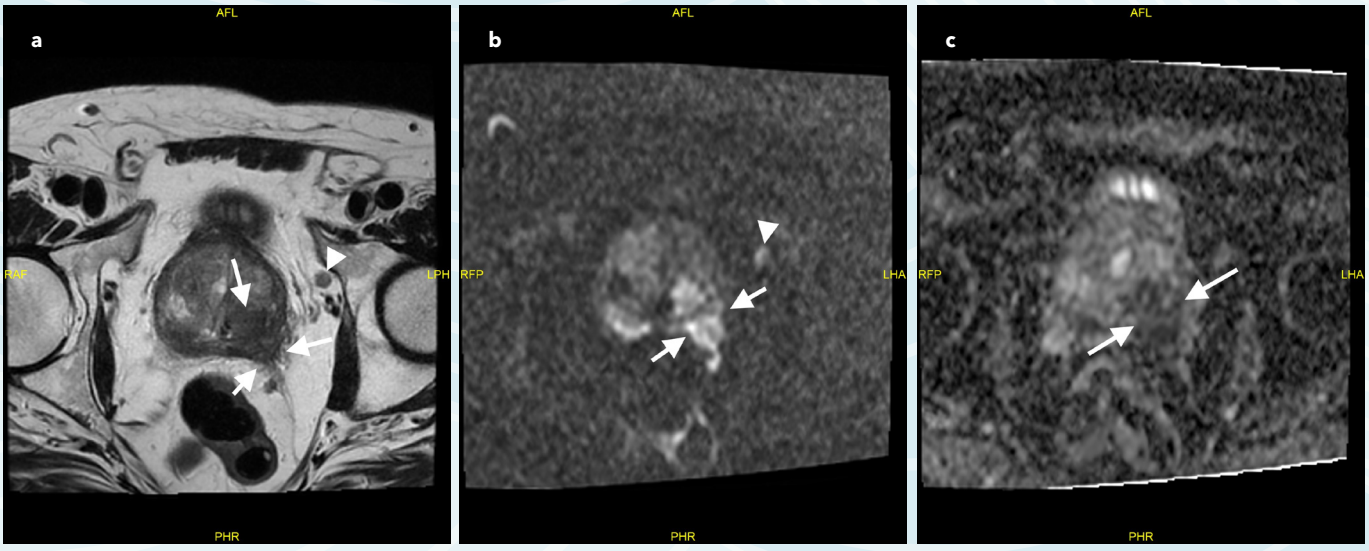
IMAGING PROSTATE CANCER

Imaging of the prostate is generally advocated within the clinical setting of a rising level of serum PSA.

Conventional imaging including computed tomography (CT) (Fig 1) and Technetium 99m (^{99}Tc)-labelled methylene diphosphonate (MDP) bone scanning (Fig 2) are used for initial staging to detect metastatic disease. Metastatic disease occurs mainly to the bones and lymph nodes; metastases may also be found in the liver, lungs, pleura, adrenal glands, ureter, peritoneum, penis, testes, and meninges.

Increased radiotracer uptake on ^{99}Tc-MDP scans reflects increase bone turnover, which may be caused by metastatic prostate cancer. However increased bone turnover may also occur with fractures, degenerative

Fig 4. a. T2-w image showing tumour extending through the postero-lateral prostatic capsule (arrows) and an enlarged lymph node (arrowhead). b. The prostatic lesion (arrows) and enlarged lymph node (arrowhead) show high signal in the DWI image. c. The prostatic tumour shows diffusion restriction (low signal - arrows) on the ADC map (Case courtesy of Dr Ian Bickle, Radiopaedia.org, rID: 84984).



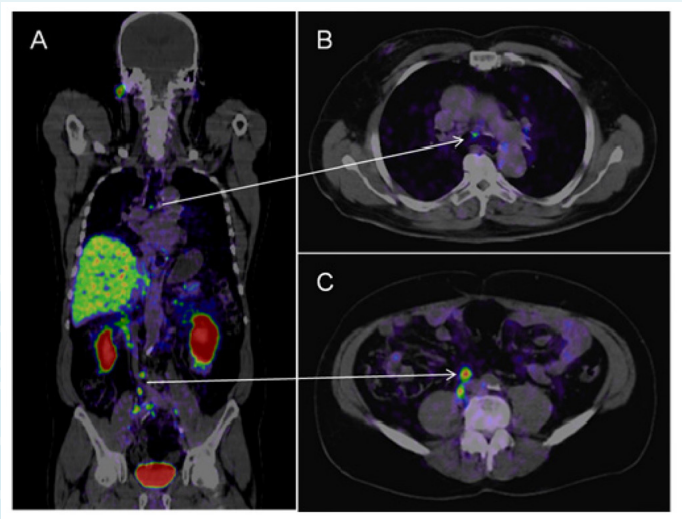


Fig 5. CT/PET Ga68 PMSA scan showing metastatic disease in small lymph nodes in the mediastinum (arrow A and B) and in the retroperitoneum (arrow A and C).

joint disease, and Paget's disease. In equivocal ^{99}Tc-MDP scans, further evaluation with skeletal radiography, CT, Magnetic Resonance Imaging (MRI) and biopsy may be required to confirm or exclude metastatic prostate cancer.

CT scanning is useful for monitoring enlarged lymph nodes, sclerotic bone metastases and visceral metastases, while MRI and ^{99}Tc-MDP scans are superior for monitoring bone metastases.[4] However, metastatic prostate cancer is often present in normal sized lymph nodes, which are missed on CT scans.[5]

CT and bone scanning are not useful for assessing the extent of local disease within the prostate and for detecting direct extracapsular extension.

Multiparametric Magnetic Resonance Imaging (MP-MRI) of the prostate is an established imaging method for assessment of loco-regional disease and for detection of recurrence within the prostate or the prostate bed (after prostatectomy).[6] MP-MRI is also useful for imaging targeted biopsy of the prostate.

Reporting of MP-MRI findings is done using a structured reporting system called Prostate Imaging – Reporting and Data System (PI-RADS). This system takes all findings seen on different MRI imaging sequences and combines them into a score that is used to guide treatment. PI-RADS scoring is based on findings seen on T2-weighted (T2-w) images, diffusion-weighted images (DWI) and dynamic contrast-enhanced (DCE) T1-weighted images. PI-RADS scores indicate the likelihood of significant cancer and range from PI-RADS 1 (very low) to PI-RADS 5 (very high). Biopsy should be considered with PI-RADS 4 or 5 scores, and observation with PI-RADS 1 or 2 lesions.

On T2-w images, prostate cancer appears as an area of low signal (Fig 3a), while on DWI it shows high signal (Fig 3b). DWI images are used to derive Apparent Diffusion Coefficient (ADC) maps that are used to detect areas of restricted diffusion associated with high cellularity that is seen in malignant lesions; suspicious lesions are seen as dark areas on ADC maps (Fig 3c). DCE imaging is used in combination with T2-w and DWI. If a lesion noted on T2-w or DWI enhances, even if the enhancement is similar to adjacent normal prostatic tissue, this is considered indicative of viable tumour (Fig 3d).

Extracapsular infiltration of prostatic cancer and lymph node metastases are also detected on MP-MRI (Fig 4).

Positron Emission Tomography (PET)/CT and PET/MRI are increasingly used for detection of local and metastatic prostate cancer. Initially radiotracers containing carbon-11 choline and fluorine-18 fluciclovine were used with PET/CT and PET/MRI with some success at detecting foci of prostate cancer. More recently gallium-68 prostate-specific membrane antigen (PMSA) radioactive PET tracers are being implemented to detect local and metastatic prostate cancer (Fig 5). These radiotracers show increased sensitivity and specificity for detecting metastatic disease such as small-volume lymph node metastases.

CONCLUSION

As is evident above, imaging of prostate cancer is a complex process, where numerous parameters are available that need to be combined to guide effective treatment. However, treatment decisions also depend on other factors including patient age, changing PSA levels, clinical history, local expertise and patient preferences.

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