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Foreword Messages

Head of Department of Anatomy

Prof. Jean Calleja Aguis

It is my pleasure to be invited to write the editorial for this issue of Minima Medica. The year 2020 will certainly remain synonymous with the COVID-19 pandemic, with all its repercussions on healthcare and society at large. More than ever, the power of social media has led to the birth of infodemiology, which is the study of dealing with a new phenomenon: the infodemic, ie the spread of mis-information. The way the media has been reporting the happenings related to the COVID-19 pandemic has highlighted the need to spread correct information, particularly related to healthcare. Certainly one way of spreading the correct information is through peer-reviewed scientific literature, which medical students and future doctors still need to critically appraise.

The COVID-19 pandemic has left many victims, and one serious side-effect has been the adverse effect on mental health. It is important to keep in mind the holistic wellbeing of every individual, as outlined in the article 'Further from the COVID-19 Pandemic: A New Health Crisis?'. Mental health is of utmost importance, and this has come to the forefront particularly in recent times. Neurological conditions are also dealt with in this issue, in articles such as 'Spinocerebellar Ataxia Type 2 and its association with Amyotrophic Lateral Sclerosis', 'Phantom Limb Syndrome', 'Parkinson's Disease' and 'Frontotemporal Dementia Case Report'.

Cancer is still generating a huge burden for citizens, cancer survivors and their families, and for health systems and society at large. Many more people are living with cancer as the result of an ageing population, unhealthy lifestyles, and unfavourable social, environmental and working conditions. This has prompted the European Union to make it one of its missions to fund more research related to cancer under the Horizon Europe Framework Programme for Research and Innovation (2021-2027): https://ec.europa.eu/info/publications/conquering-cancer-mission-possible_en. In this edition, cancer is of course one of the topics, through articles such as: 'Bloom Syndrome: an example of how genomic instability leads to cancer'; 'The effects of different diets on Colorectal Cancer; and 'Vitamin D Receptor and Cancer'. Having a healthy diet and lifestyle is also very important for managing irritable bowel syndrome as well as preventing colorectal cancer, as mentioned in two of the articles.

Fetal development and neonatology are also important topics which are dealt with in two other articles, namely 'Neonatal Hypoglycemia: A review' and 'Pathophysiology of Hydrops Fetalis'. Despite all the material which needs to be covered in the medical curriculum, embryology still plays a very integral part in understanding intrauterine development and the impact after birth, both in the short- and long term, and even in future generations of the offspring.

The COVID-19 has led to dramatic changes in education, with the distinctive rise of e-learning, whereby teaching and learning is undertaken remotely. Student self-learning, by undertaking research, increases retention of information, and using digital platforms, can lead to sharing of this information through peer teaching. That is why initiatives taken up by medical students such as Minima Medica, are highly commendable and encouraged. Keep it up!

SCOME Officer
Matthew Buttigieg

The MMSA's Minima Medica Journal made its resurgence last year during MMSA SCOME's Research Conference following a hiatus, prior to which it was known as Minima Medicamenta. The relaunch, coordinated by then Medical Education Officer and current MMSA President, Gloria Montebello, included 6 literature reviews and case reports and was extremely well received.

I am honoured to be launching the 2021 edition of Minima Medica, paving the path to the Journal's revival as an annual Journal. Minima Medica is one of the first, if not the first opportunity for our fellow medical students to delve into the world of publications and academia. With a total of 13 articles, more than double the number present in last year's edition, the 2021 edition of Minima Medica publication sees 15 future doctors publish literature reviews and case reports, which have all been reviewed by established Academics and Professors at the University of Malta.

I am indebted to the editors and SCOME Publications Coordinators for the term Bernardette Mangion & Jennifer Xuereb, as well as the Medical Education Assistant Nicholas Galea, without whom the publication of this journal would not be possible. I would also like to thank MMSA's Public Relations Officer Mariah Borg for the design of the Journal, each and every author who submitted their article and each Academic who accepted to review the students' work.

Being greatly contended by the interest that his journal has gathered so far, I hope that is found to be an interesting and fruitful read by clinicians, academics and students alike.

Editors

Bernardette Mangion & Jennifer Xuereb

Dear readers,

We are greatly enthusiastic and appreciative that we were given the opportunity to present you with this year's publication of Minima Medica! The aim of this journal is to allow medical students a platform where they may refine, publish and share their work. Furthermore, within this journal one may find an array of captivating articles and literature reviews.

To be able to achieve the greatest accuracy, the process of publication required both time and dedication from the authors, who first had to have their work reviewed by a tutor. This was followed by amending their submission according to suggestions from external reviewers. Hence, we would also like to commend external professionals as this publication would not have been made possible without their input.

We would like to show our gratitude towards Prof Calleja Agius who kindly took time to write our forward message which introduced each article. Moreover, we would also like to thank our SCOME officer Matthew Buttigieg for his continual guidance and motivation. Lastly, we would like to applaud each author for their great effort and contribution.

Literature Reviews

Author:
Elizabeth Grech

Reviewers:
Dr. Ruben Cauchi
Prof. Neville Vassallo

Amyotrophic Lateral Sclerosis (ALS)

Abstract

Amyotrophic lateral sclerosis (ALS) is a motor neuron disorder with a terminal outcome, the pathophysiology of which is not yet clearly understood. There are various subtypes of ALS and factors related both to the environment and to genetics which play a role in the development of the condition. This article will give a general overview of ALS and will specifically discuss some of the different types of ALS, its possible causes, neuropathology, signs and symptoms and its progression. Therapeutic interventions and a brief mention of the future of ALS research will also be outlined.

Keywords

Amyotrophic lateral sclerosis (ALS), motor neuron disease, neurodegeneration, upper andlower motor neurons, frontotemporal dementia

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative condition which is, as yet, incurable. Deterioration of motor neuron occurs in ALS (1,2). Motor neurons have cell bodies which are either present within the motor cortex of the brain, the brainstem or the spinal cord. The axon fibre of motor neurons projects to the spinal cord or to target glands and muscles in order to control them directly or indirectly (3).

Upper motor neurons (UMNs) and lower motor neurons (LMNs) are the two types of motor neurons that exist. LMNs innervate effector muscles directly and their cell bodies are located inside the grey matter of the spinal cord and brain stem. UMNs control LMN activity and form the descending corticospinal and corticobulbar tracts (4). The axons of LMNs are efferent fibres which conduct signals from the

spinal cord to target glands or muscles (5). The motor neuron system is depicted in Figure 1.

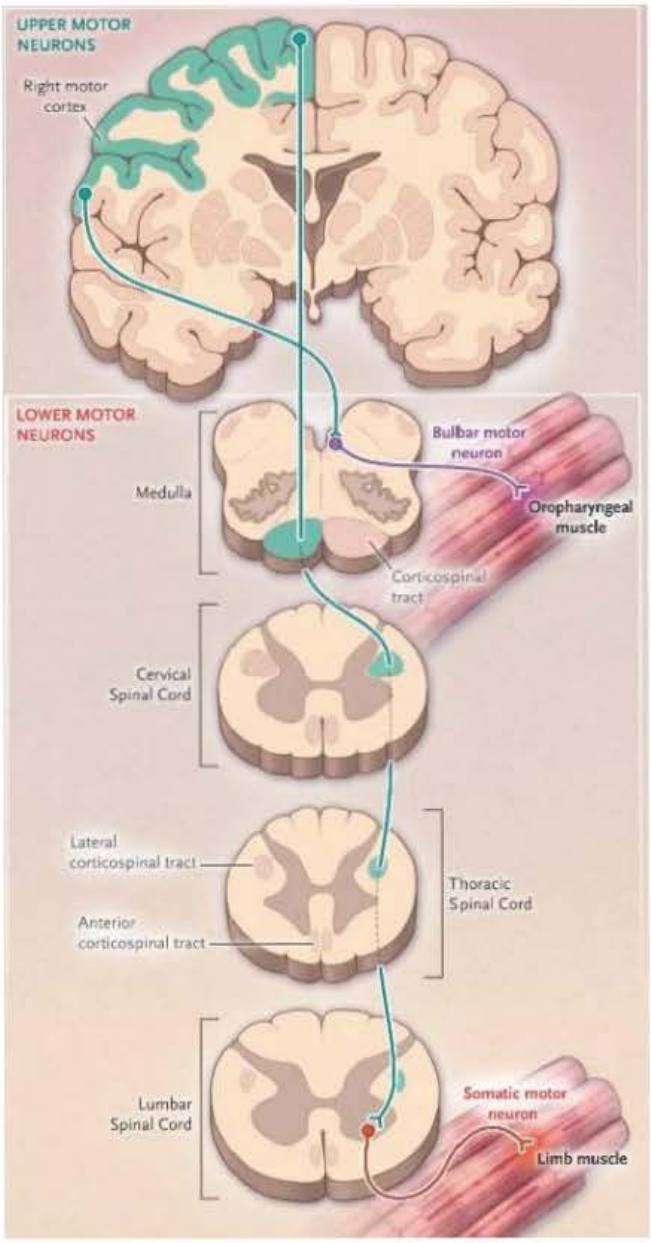

Figure 1 - The motor system showing UMNs and LMNs. Adapted from Brown & Al-Chalabi, 2017

Progressive UMN death along with LMN death takes place throughout the course of this disease, resulting in a variety of symptoms (1,2).

ALS may be familial or sporadic. Familial ALS (fALS) occurs when the diagnosed individual has at least one affected relative, while in sporadic ALS (sALS) there is no known affected relative. The incidence of ALS decreases in people aged 80 years and above (6,7).

Epidemiology

The registry European Amyotrophic lateral sclerosis (EURALS) showed an estimated incidence of ALS of 2.2 per 100,000 person-years (8). Incidence rates of ALS range from 1.1per 100,000 per year to 2.2 per 100,000 per year in difference parts of Europe (9).

fALS is distinguished from sALS as it has an earlier mean age of onset, around 46 years as opposed to 56 years in sALS (10).

The overall male-to-female ratio of ALS is 1.5 - 2:1 making ALS more common in men (11).

Classification of ALS

ALS is classified as being part of a group of MNDs. ALS is the most common MND and it is the predominant MND in adults (12,13).

There are two main forms of classical ALS:

1. Spinal onset ALS, or limb onset ALS and
2. Bulbar onset ALS (14).

Spinal onset ALS presents with upper and lower limb weakness at first, as shown in Figure 2(15). The initial presentation of bulbar onset ALS includes loss of ability to speak, swallow and chew as per Figure 2 (16). A better prognosis is generally seen in spinal onset ALS as is shown in Figure 3 (17)

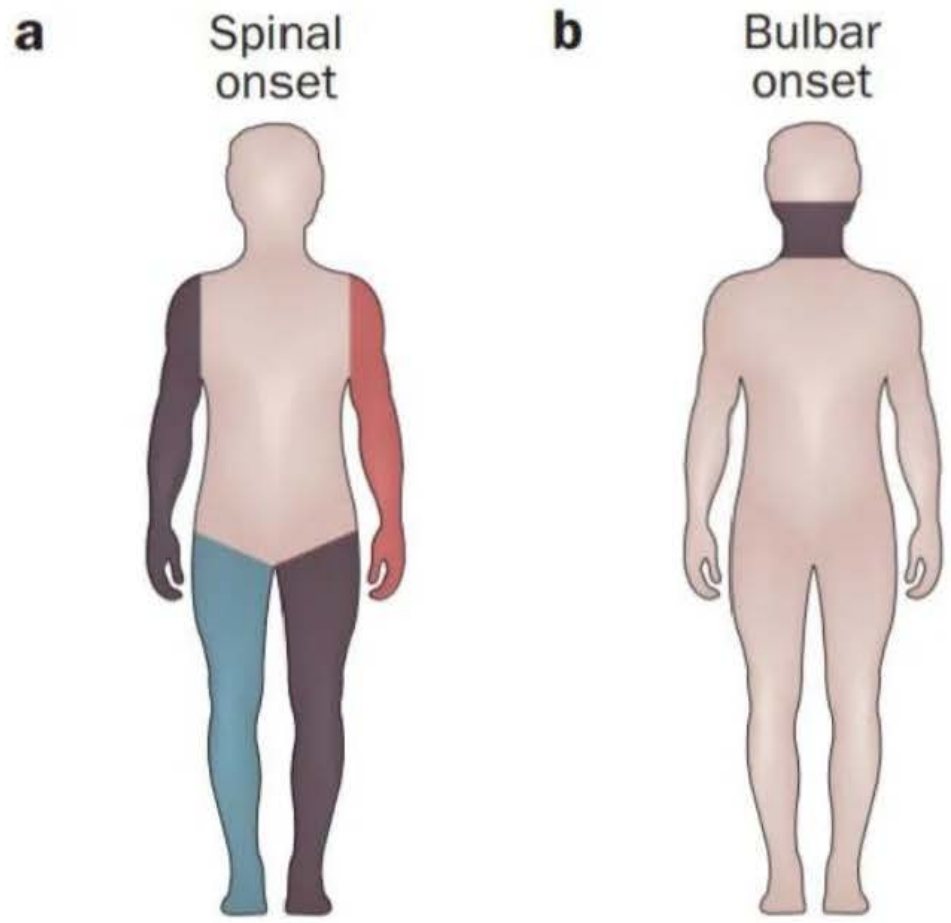

Figure 2 - Patterns of motor involvement in spinal onset ALS vs bulbar onset ALS. More severe involvement is illustrated using darker shading. Adapted from Swinnen & Robberecht, 2014.

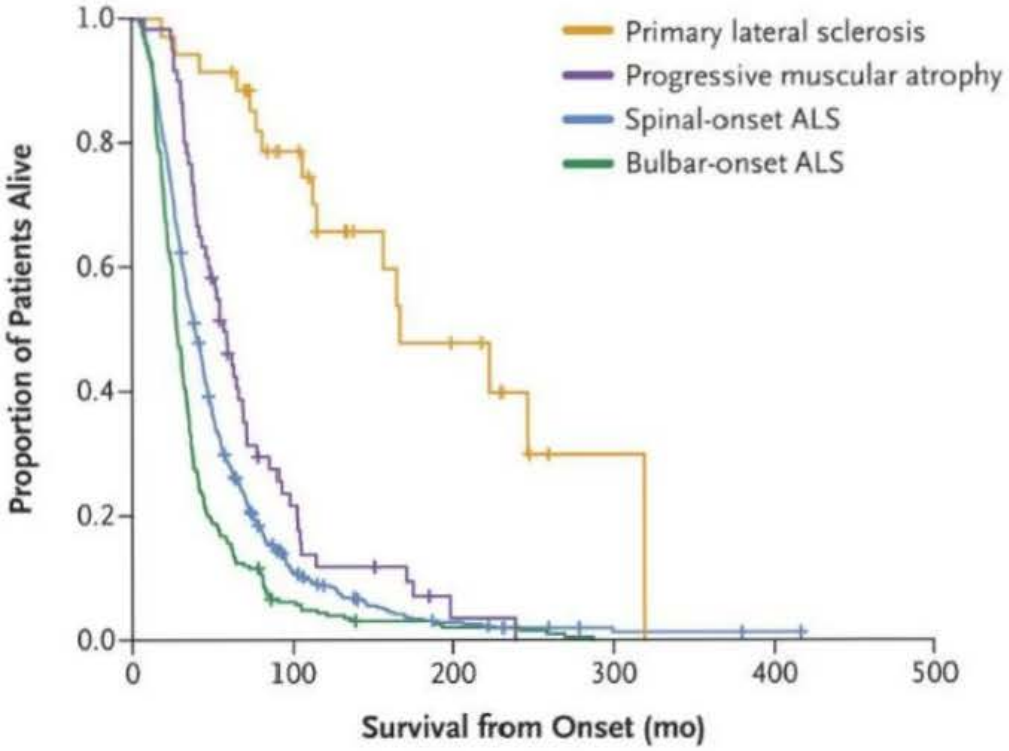

Figure 3 - Graph showing proportion of patients alive against survival from onset (months). Adapted from Brown & Al-Chalabi, 2017.

Regional ALS

When symptoms of ALS affect only one spinal cord region for a year or more, the condition is termed a regional variant of ALS. There is slower progression than classical ALS and survivaltends to be longer (18).

Age of Patient at Onset of ALS

Age at onset can also be used to classify the type of ALS. Approximately 10% of all ALS cases start before patients reach 45 years of age. This is considered young onset ALS. Juvenile ALS occurs in 1% of cases and is said to occur when ALS appears before the age of 25 (6,16). Sudden functional decline and lower longevity are common in late onset ALS, which occurs after the age of 65 (19).

Causes of ALS

Despite the number of genes that are known to be linked with ALS as well as a better understanding of the various cellular processes that contribute to the disease's pathogenesis, the exact cause of ALS remains, as yet, undetermined (20). It is thought that a combination environmental factors such as smoking, body mass index and

metal and pesticide exposure, as well as genetic factors contribute to the incidence of ALS (21).

Genetics of ALS

Around 10% of all ALS cases are familial, (22,23). fALS and sALS cannot be distinguished clinically (22). Recent studies have shown that the burden of ALS-associated genes in sALS appear to be lower than previously estimated (23).

Four specific genes are associated with most cases of fALS:

1. C9orf72 (chromosome 9 open reading frame 72) - 40%
2. SOD1 (Superoxide dismutase [Cu-Zn]) - 20%
3. FUS (fused in sarcoma gene) - 1–5%
4. TARDBP (TAR DNA Binding Protein) - 1–5%

More than one gene must be affected for ALS to occur due to the oligogenic inheritance ofALS. At least 25 genes have been linked to fALS, sALS or both since 1990 (25).

Three main pathways have been identified in which genes associated with ALS cluster:

1. Disturbed RNA metabolism
2. Proteostasis
3. Axonal transport defects (26)

ALS and Frontotemporal Dementia

ALS and frontotemporal dementia (FTD) are better defined as being part of a disease spectrum. This spectrum came about due to the pathological, clinical and genetic similarities between the two diseases. ALS with no cognitive involvement is known as pure ALS while pure FTD excludes any signs of MND. These two conditions are found at opposite poles of the continuum (7).

Neuropathology

A signature feature of ALS is dysfunction of both UMNs and LMNs (27). A pathognomonic feature of ALS is the aggregation of certain proteins within the cytosol of motor neurons. These are termed inclusion bodies (15,28).

TDP-43 protein may aggregate abnormally within the cytoplasm. This occurs in around 97%of ALS cases while it is also seen in up to half of those with FTD (29). The inclusion bodies which deposit in the brain and spinal cord of patients who suffer from ALS and FTD contain hyper-phosphorylated and ubiquitinated TDP-43 aggregates (28). UMN and LMN cell death which follows axonal degeneration and neuromuscular junction loss is a neuropathological signature of ALS (31).

Atrophy of peripheral muscles and of the motor cortex as well as corticobulbar and corticospinal tract sclerosis and hypoglossal nerve thinning are gross pathological features of ALS (15).

Signs and Symptoms

ALS results in muscle atrophy, weakness and spasm which affect the entire body. Both UMN and LMN signs may be present since both are affected in ALS. UMN signs include hyperreflexia, spasticity and slow movements whereas LMN signs include muscle wasting and decreased muscle tone, the presence of fasciculations and hyporeflexia (30). Upper limb onset typically occurs in the dominant hand and seems to preferentially involve the thenar muscles(32). The anterior tibial muscle seems to be the starting point of lower limb onset (33). Muscle weakness often starts in the distal limb muscles (34).

Symptoms of ALS usually only affect one section of the spinal cord initially before progressing to other regions (16). Control of all intentional motor function may be lost (35). The most frequently reported cognitive issues in ALS are problems with language, executive functions, social cognition as well as verbal memory (36).

Most ALS patients experience pain which may be a result of nerve damage (neuropathic),muscle cramps and spasticity. Back, neck, shoulder pain and pressure ulcers also contribute to pain in ALS (37).

Initial symptoms in bulbar onset ALS include dysfunction related to speech and swallowing. Fasciculations and tongue wasting are common in bulbar ALS (6). Some of the observable signs of ALS are shown in Figure 4 and Figure 5.

Diagnosis of ALS

Diagnosis of ALS is made clinically. The presence of UMN and LMN signs are integral to the diagnosis of ALS (30). LMN involvement can be detected by needle electromyography (EMG)before it becomes clinically detectable. This extends the physical examination and allows early diagnosis (38). Positron emission tomography (PET) scanning may detect hypometabolism within frontotemporal lobes of patients with ALS (39).

Although various biomarkers are being explored as potential diagnostic features, none are currently commonly used in medical practice (40, 41). Examples of such biomarkers obtained from cerebrospinal fluid include cystatin C and peptic fragment of the nerve growth factor inducible (VGF) (42).

Therapeutic Interventions

ALS currently has no cure. Treatment is oriented towards easing symptoms and supportive management, the goal being to provide a better quality of life (QoL) and prolonging life (14).

ALS Drug Treatment

A number of medications are used to manage various symptoms in ALS (43). Medications such as riluzole, a glutamate antagonist, slow disease

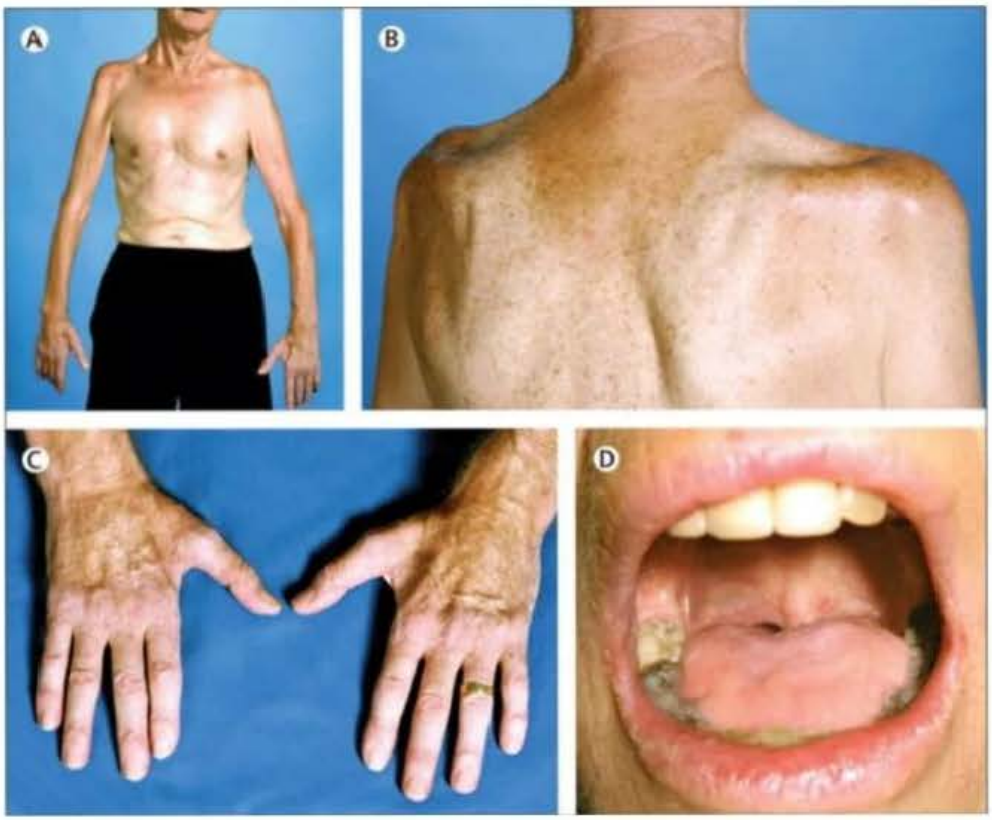

Figure 4
Panel A - Upper limb muscle atrophy typical of flail arm syndrome in ALS
Panel B - Atrophy of infraspinatus, supraspinatus and deltoid in ALS patient
Panel C - Thenar muscle wasting in ALS patient
Panel D - Tongue atrophy in patient with bulbar onset ALS
Adapted from Kiernan et al., 2011

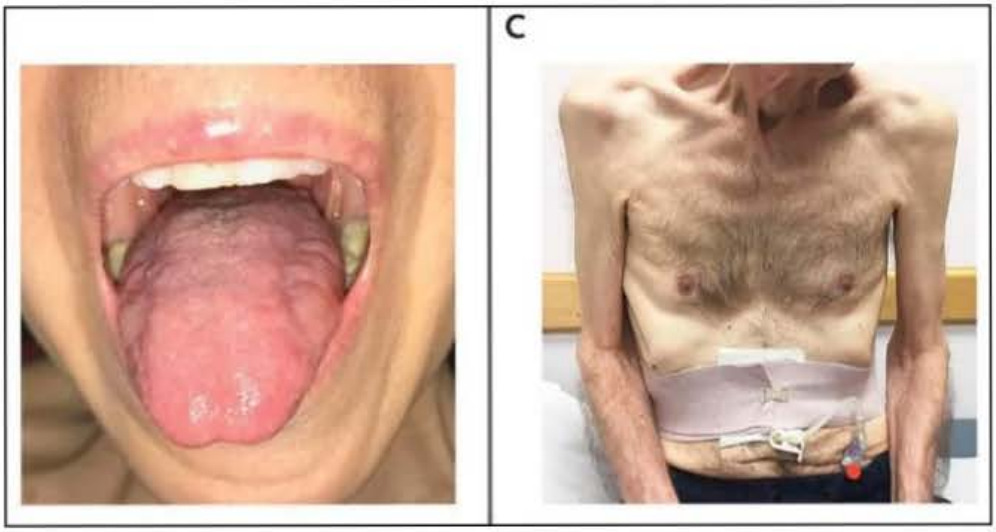

Figure 5
Panel A - Lateral atrophy of the tongue in an ALS patient
Panel B - Atrophied upper limbs in flail arm syndrome in ALS

progression and may prolong survival by two to three months (44,45). The drug edaravone, an antioxidant, may modestly decrease the rate of decline in function in only a very small group of patients who meet very specific criteria (46).

The antispasmodic effects of the oral drugs baclofen and tizanidine are employed to treat muscle spasms (15). Botulinum toxin type A injection (BTX-A) is used to relieve muscle spasticity (47). Muscle cramps can be relieved by gabapentin and carbamezapine (48,49)

Breathing Support

Non-Invasive Ventilation

The main treatment for respiratory depression in ALS is non-invasive ventilation (NIV) and this was the first treatment for ALS which was shown to improve QoL and survival (35,15). NIV has been found to extend survival longer than riluzole and greatly improves QoL (50).

Invasive Ventilation

In advanced ALS, NIV becomes insufficient and invasive ventilation becomes another option(35). Invasive ventilation is inserted past the upper airways by means of a tracheostomy. A tube is then inserted and connected to a ventilator (51).

Palliative Care

Palliative care does not treat the underlying disease but rather, attempts to ease symptoms and increase QoL. This type of care should begin soon after a patient is diagnosed with ALS(52). Discussing end-of-life options with ALS patients allows them time to decide on their preferences and prevents unwanted interventions later on, especially when communication becomes more difficult (53,15).The median survival for ALS is slightly less than 3 years from onset of symptoms (54). Most deaths in patients with ALS are generally due to respiratory failure or pneumonia (6).

Conclusion: The Future of ALS Research

The aetiology of ALS has still not been fully defined and options for treatment are limited (55).This is so because it is difficult to design treatments without knowing the exact pathophysiology of the disease (56). A greater understanding of the genes and biology involved in the pathophysiology of ALS is highly desirable (55).

References

1. Caplliure-Llopis J, Peralta-Chamba T, Carrera-Juliá S, Cuerda-Ballester M, Drehmer-Rieger E, López-Rodriguez M & Rubia Ortí J (2019). Therapeutic alternative of theketogenic Mediterranean diet to improve mitochondrial activity in Amyotrophic LateralSclerosis (ALS): A Comprehensive Review. Food Science & Nutrition; DOI:10.1002/fsn3.1324.

2. Batra G, Jain M, Soloman Singh R, Sharma A, Singh A, Prakash A & Medhi B (2020).Novel therapeutic targets for amyotrophic lateral sclerosis. The Indian Journal ofPharmacology; DOI: 10.4103/ijp.IJP_823_19: 10.4103/ijp.IJP_823_19.

3. Tortora G (2014). Principles of anatomy & physiology, 14th edition, 14th edn. John Wiley& Sons, Inc., New Jersey.

4. Crossman. (2015). Neuroanatomy: AN ILLUSTRATED COLOUR TEXT, 5th edn. Elsevier.

5. Schacter D, Gilbert D & Wegner D (2011). Psychology, 2nd edn. Worth, New York.

6. Kiernan M, Vucic S, Cheah B, Turner M, Eisen A, Hardiman O, Burrell J & Zoing M (2011).Amyotrophic lateral sclerosis. The Lancet 377, 942-955.

7. Swinnen B & Robberecht W (2014). The phenotypic variability of amyotrophic lateral sclerosis. Nature Reviews Neurology 10, 661-670.

8. Logroscino G, Piccininni M. Amyotrophic Lateral Sclerosis Descriptive Epidemiology: The Origin of Geographic Difference. Neuroepidemiology. 2019;52(1-2):93-103.

9. European Amyotrophic lateral sclerosis (EURALS) – ENMC [Internet]. Enmc.org. 2020[cited 9 December 2020]. Available from: https://www.enmc.org/download/europeanamyotrophic-lateral-sclerosis-eurals/

10. Turner M, Al-Chalabi A, Chio A, Hardiman O, Kiernan M, Rohrer J et al. Genetic screening in sporadic ALS and FTD. 2020.

11.How does the incidence of amyotrophic lateral sclerosis (ALS) vary by sex? [Internet].Medscape.com. 2020 [cited 9 December 2020]. Available from:https://www.medscape.com/answers/1170097-81849/how-does-the-incidence-ofamyotrophic-lateral-sclerosis-als-vary-by-sex

12. Yedavalli V, Patil A & Shah P (2018). Amyotrophic Lateral Sclerosis and its Mimics/Variants: A Comprehensive Review. Journal of Clinical Imaging Science; DOI:10.4103/jcis.JCIS_40_18.

13. Cacciottolo R, Ciantar J, Lanfranco M, Borg R, Vassallo N, Bordonné R & Cauchi R (2019).SMN complex member Gemin3 self-interacts and has a functional relationship with ALS linked proteins TDP-43, FUS and Sod1. Scientific Reports; DOI: 10.1038/s41598-019-53508-4.

14. van Es M, Hardiman O, Chiò A, Al-Chalabi A, Pasterkamp R, Veldink J & van den Berg L(2017). Amyotrophic lateral sclerosis. The Lancet 390, 2084-2098.

15. Hardiman O, Al-Chalabi A, Chiò A, Corr E, Logroscino G, Robberecht W, Shaw P,Simmons Z & van den Berg L (2017). Amyotrophic lateral sclerosis. Nature Reviews Disease Primers; DOI: 10.1038/nrdp.2017.71.

16. Grad L, Rouleau G, Ravits J & Cashman N (2017). Clinical Spectrum of Amyotrophic Lateral Sclerosis (ALS). Cold Spring Harbor Perspectives in Medicine 7, a024117.

17. Chiò A, Calvo A, Moglia C, Mazzini L & Mora G (2011). Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population-based study. Journal of Neurology, Neurosurgery & Psychiatry 82, 740-746.

18. Jawdat O, Statland J, Barohn R, Katz J & Dimachkie M (2015). Amyotrophic Lateral Sclerosis Regional Variants (Brachial Amyotrophic Diplegia, Leg Amyotrophic Diplegia, and Isolated Bulbar Amyotrophic Lateral Sclerosis). Neurologic Clinics 33, 775-785.

19. Tard C, Defebvre L, Moreau C, Devos D & Danel-Brunaud V (2017). Clinical features of amyotrophic lateral sclerosis and their prognostic value. Revue Neurologique 173, 263-272.

20. Mejzini R, Flynn L, Pitout I, Fletcher S, Wilton S & Akkari P (2019). ALS Genetics, Mechanisms, and Therapeutics: Where Are We Now?. Frontiers in Neuroscience; DOI:10.3389/fnins.2019.01310

21. Wingo T, Cutler D, Yarab N, Kelly C & Glass J (2011). The Heritability of Amyotrophic Lateral Sclerosis in a Clinically Ascertained United States Research Registry. PLoS ONE6, e27985.

22. He J, Mangelsdorf M, Fan D, Bartlett P & Brown M (2014). Amyotrophic Lateral Sclerosis Genetic Studies. The Neuroscientist 21, 599-615.

23. Boylan K (2015). Familial Amyotrophic Lateral Sclerosis. Neurologic Clinics 33, 807-830.

24. Gibson S, Downie J, Tsetsou S, Feusier J, Figueroa K, Bromberg M et al. The evolving genetic risk for sporadic ALS. Neurology. 2018;89(3):226-233.

25. Renton A, Chiò A & Traynor B (2013). State of play in amyotrophic lateral sclerosisgenetics. Nature Neuroscience 17, 17-23.

26. Chia R, Chiò A, Traynor B. Novel genes associated with amyotrophic lateral sclerosis:diagnostic and clinical implications. The Lancet Neurology. 2018;17(1):94-102.

27. Robberecht W & Philips T (2013). The changing scene of amyotrophic lateral sclerosis.Nature Reviews Neuroscience 14, 248-264.

28. Prasad A, Bharathi V, Sivalingam V, Girdhar A & Patel B (2019). Molecular Mechanisms of TDP-43 Misfolding and Pathology in Amyotrophic Lateral Sclerosis. Frontiers in Molecular Neuroscience; DOI: 10.3389/fnmol.2019.00025.

29. Nguyen H, Van Broeckhoven C & van der Zee J (2018). ALS Genes in the Genomic Eraand their Implications for FTD. Trends in Genetics 34, 404-423.

30. Kumar P, Clark M, Zammitt N, O'Brien A. Essentials of Kumar & Clark's clinical medicine.[S.l.]: Elsevier; 2018.

31. Cappello V, Francolini M. Neuromuscular Junction Dismantling in Amyotrophic LateralSclerosis. International Journal of Molecular Sciences. 2017;18(10):2092.

32. Turner M, Wicks P, Brownstein C, Massagli M, Toronjo M, Talbot K et al. Concordancebetween site of onset and limb dominance in amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery & Psychiatry. 2010;82(8):853-854

33. Hu F, Jin J, Chen Q, Kang L, Jia R, Qin X et al. Dissociated lower limb muscle involvement in amyotrophic lateral sclerosis and its differential diagnosis value. Scientific Reports.2019;9(1).

34. Wijesekera L, Leigh P. Amyotrophic lateral sclerosis. Orphanet Journal of Rare Diseases.2009;4(1):3.

35. Hobson E & McDermott C (2016). Supportive and symptomatic management of amyotrophic lateral sclerosis. Nature Reviews Neurology 12, 526-538.

36. Beeldman E, Raaphorst J, Klein Twennaar M, de Visser M, Schmand B & de Haan R(2015). The cognitive profile of ALS: a systematic review and meta-analysis update.Journal of Neurology, Neurosurgery & Psychiatry 87, 611-619.

37. Chiò A, Mora G & Lauria G (2017). Pain in amyotrophic lateral sclerosis. The Lancet Neurology 16, 144-157.

38. Joyce N, Carter G. Electrodiagnosis in Persons With Amyotrophic Lateral Sclerosis.PM&R. 2013;5:S89-S95.

39. Mittal B, Abrar M, Singh B, Harisankar C, Agrawal K, Bhattacharya A et al. FDG-PET findings in fronto-temporal dementia: A case report and review of literature. Indian Journal of Nuclear Medicine. 2011;26(2):96.

40. Xu Z, Henderson R, David M & McCombe P (2016). Neurofilaments as Biomarkers for Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis. PLOS ONE 11,e0164625.

41. Vu L & Bowser R (2016). Fluid-Based Biomarkers for Amyotrophic Lateral Sclerosis.Neurotherapeutics 14, 119-134.

42. Pasinetti G, Ungar L, Lange D, Yemul S, Deng H, Yuan X et al. Identification of potentialCSF biomarkers in ALS. Neurology. 2006;66(8):1218-1222.

43. Orrell R (2010). Motor neuron disease: systematic reviews of treatment for ALS and SMA.British Medical Bulletin 93, 145-159

44. Miller R, Mitchell J & Moore D (2012). Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database of Systematic Reviews; DOI:10.1002/14651858.cd001447.pub3.

45. de Paula C, Gonçalves B & Vieira L (2015). An Overview of Potential Targets for Treating Amyotrophic Lateral Sclerosis and Huntington's Disease. BioMed Research International2015, 1-7.

46. Abe K et al. (2017). Safety and efficacy of edaravone in well-defined patients withamyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. TheLancet Neurology 16, 505-512.

47. Marvulli R, Megna M, Citraro A, Vacca E, Napolitano M, Gallo G et al. Botulinum Toxin Type A and Physiotherapy in Spasticity of the Lower Limbs Due to Amyotrophic Lateral Sclerosis. Toxins. 2019;11(7):381.

48. Serrao M, Rossi P, Cardinali P, Valente G, Parisi L, Pierelli F. Gabapentin Treatment for Muscle Cramps: An Open-Label Trial. Clinical Neuropharmacology. 2000;23(1):45-49.

49. Walling A. Amyotrophic Lateral Sclerosis: Lou Gehrig's Disease [Internet]. Aafp.org. [cited11 December 2020]. Available from: https://www.aafp.org/afp/1999/0315/p1489.html

50. Radunovic A, Annane D, Rafiq M, Brassington R & Mustfa N (2017). Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database of Systematic Reviews; DOI: 10.1002/14651858.cd004427.pub4.

51. Soriani M & Desnuelle C (2017). Care management in amyotrophic lateral sclerosis. Revue Neurologique 173, 288-299.

52. Andersen P, Abrahams S, Borasio G, de Carvalho M, Chiò A, Van Damme P, HardimanO, Kollewe K, Morrison K, Petri S, Pradat P, Silani V, Tomik B, Wasner M & Weber M(2011). EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis(MALS) - revised report of an EFNS task force. European Journal of Neurology 19, 360-375.

53. Connolly S, Galvin M & Hardiman O (2015). End-of-life management in patients with amyotrophic lateral sclerosis. The Lancet Neurology 14, 435-442.

54. Gibson S, Downie J, Tsetsou S, Feusier J, Figueroa K, Bromberg M et al. The evolving genetic risk for sporadic ALS. Neurology. 2018;89(3):226-233.

55. Clerc P, Lipnick S & Willett C (2016). A look into the future of ALS research. Drug Discovery Today 21, 939-949.

56. Benatar M, Boylan K, Jeromin A, Rutkove S, Berry J, Atassi N & Bruijn L (2015). ALS biomarkers for therapy development: State of the field and future directions. Muscle &Nerve 53, 169-182

Author:
Francesca Farrugia

Reviewers:
Dr. Duncan Ayers
Dr. Christian Scerri

Bloom Syndrome: an example of how genomic instability leads to cancer

Abstract

Bloom Syndrome (BS) is an autosomal recessive disorder whose phenotype consists of short height, a facial erythematous rash, UV sensitivity, microcephaly, and a narrow face. Cases have been documented all over the world but seem to be prevalent in individuals of Ashkenazic Jewish descent. The underlying cause of this condition is a mutation in the BLM gene on chromosome 15, which codes for the helicase enzyme, BLM. This protein is involved in DNA repair and acts with p53 to initiate apoptosis. Molecular analyses reveal several chromosomal breaks and sister chromatid exchanges that are around 10 times more frequent than in normal cells. These observations are thought to be a result of an alternative pathway which tries to resolve stalled replication forks during the process of DNA replication, hence sparing the cells from apoptosis. This primitive evolutionary survival mechanism allows some BS cells to survive, but at the price of an increased incidence of malignancies.

List of Abbreviations

BS	Bloom Syndrome
GH	Growth Hormone
IGF1	Insulin-like Growth Factor 1
SCE	Sister Chromatid Exchange
SDS	Standard Deviation Score
SGA	Small for Gestational Age
RTS	Rothmund-Thomson Syndrome
WS	Werner Syndrome

Introduction

Bloom syndrome (BS) is a rare autosomal recessive disorder that was first identified in 1954 by Dr David Bloom (1). One of the most notable features of BS is the short stature of affected individuals that persists throughout their lifetime. Infants are small for their gestational age (SGA) and even though the post-natal growth rate increases steadily, the overall size of the child is still significantly below that of its peers. However, other developmental milestones, including walking and talking, were recorded at similar ages to their unaffected peers. Another characteristic feature of BS is an erythematous rash along the butterfly region of the face (cheeks and nose) that is commonly seen in infancy but can appear later in life (figures 1 & 2). Individuals with BS also have an increased sensitivity to sunlight, which may turn an already present rash into a chronic lesion. Additionally, the head circumference is smaller than usual, the face is narrow, and patients have a shrill voice. Apart from their physical appearance, BS patients also have a higher predisposition to certain diseases, chiefly chronic lung disease, diabetes mellitus, thyroid imbalances and over 100 types of cancer (2–4).

The roots of this disorder can be traced to the BLM gene on chromosome 15 at the locus 15q26.1. BLM is a protein that belongs to the RecQ family of helicases. DNA helicases are enzymes that unwind DNA during the process of DNA replication.

A loss-of-function mutation in both BLM alleles renders the individual homozygous recessive for BS (Ellis et al., 1995). Defects in the RecQ helicase family can give rise to a group of autosomal recessive disorders, namely BS, Werner's Syndrome (WS), Rothmund-Thomson Syndrome (RTS). These syndromes are characterised by genetic instability and hence, the risk of developing malignancies is greatly increased (5).

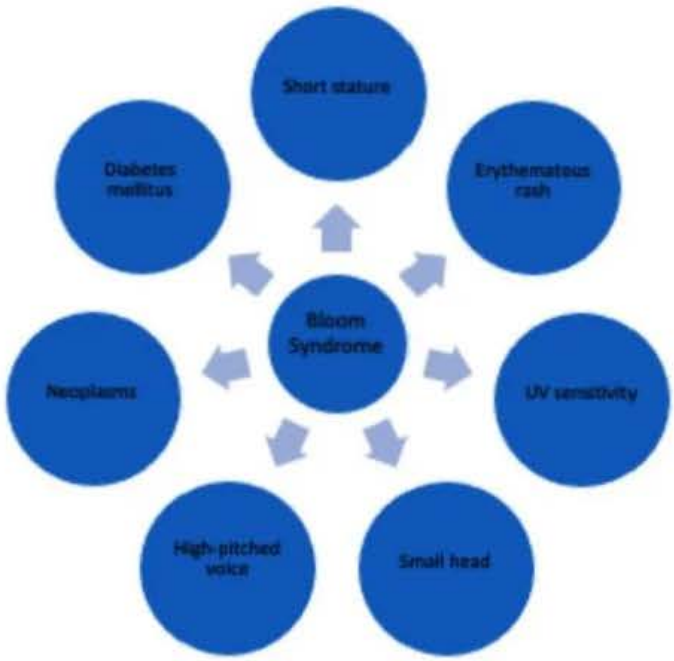

Figure 1: Common features of Bloom Syndrome

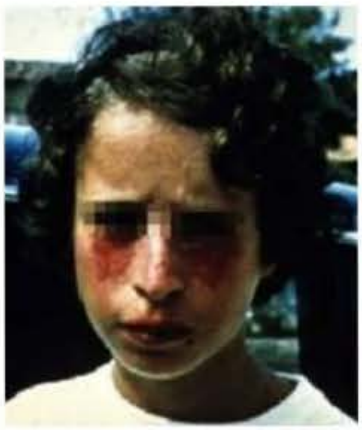

Figure 2: Child with Bloom Syndrome showing the characteristic facial erythematous rash

2. Epidemiology

Mutations in the BLM gene are prevalent in people of Ashkenazic Jewish descent (2). A genetic analysis of 1491 individuals of Ashkenazi Jewish descent with no known history of BS revealed that 1 in 107 individuals were carriers of the BLMAsh mutation. This is comparable to other conditions affecting Ashkenazic Jews such as Niemann-Pick disease (1 in 80 carrier frequency) and Fanconi Anaemia Type C (1 in 90 carrier frequency) and could lead to the inclusion of BS in screening programmes for these individuals (6). As of 2009, 26% of affected individuals known to the BS Registry are of Jewish descent, while the rest are non-Jewish (7).

3. Incidence and Types of Neoplasms in BS Patients

Individuals with BS tend to develop some form of neoplasia at an early age when compared to unaffected individuals of the same age group. In fact, it is not uncommon for children with unexplained short height and who develop rare cancers at an early age to be screened for BS. As of 1996, 100 different types of neoplasms were recorded in 71 out of 168 individuals in the Bloom Syndrome Registry. This contrasts to other syndromes that usually have a predilection for a small group of neoplasms. Interestingly, a pattern of neoplasms can be observed throughout the patients' lifetime. Leukaemias and lymphomas are the most common malignancies of childhood. Conversely, solid carcinomas are more predominant in adulthood and appear at an earlier age than in the normal population. Furthermore, patients may develop more than one primary tumour, with up to five primaries being recorded (3).

4. Molecular Basis of Disease

4.1. Chromosomal Abnormalities in BS Cells

Microscopic chromosomal analysis of BS cells reveals increased sister chromatid exchanges (SCEs) during the S-phase of the cell cycle. Sites of increased chromosomal exchange give rise to gaps and breaks in the chromosome, hence classifying BS as a chromosomal breakage syndrome.

The basis of diagnosing BS using cytogenetic analysis is a frequency of SCEs which is 10 times greater than in the normal population (8).

4.2. Proposed Roles of BML and other RecQ Helicases

The RecQ helicases unwind DNA in a 3' to 5' direction and require energy in the form of ATP. Moreover, they are the only known group of enzymes that can unwind G-quadruplex DNA. This is a highly stable structure which is formed by several planar guanine tetrads (G4) stacked on top of each other. Replication or recombination events occurring before mitosis could expose G-rich regions of DNA, thus allowing for the formation of highly stable G-tetrads instead of the usual Watson-Crick base pairs. In a normal cell, functional BLM can dissolve the tetrad, thereby allowing replication to continue. However, mutant RecQ enzymes are unable to unwind G-quadruplexes in DNA, which can halt the replication process and produce stalled recombination intermediates (9).

Additionally, BLM acts in association with human topoisomerase isozyme topo IIIα. It is thought that RecQ and topo IIIα act together during DNA recombination to stop unsuitable strands of DNA from participating in recombination events. The duo can potentially unwind the improper recombination intermediate and restore the original DNA strands (10).

4.3. BLM and Apoptosis

Several experiments done in vitro have shown that BS cells are unable to perform apoptosis properly. A study by Wang et al. found that BS fibroblasts show ineffective apoptosis mediated by p53. Interestingly, the introduction of p53 into BS fibroblasts did not improve the initiation of apoptosis. In contrast, the re-introduction of the functional BLM protein returns the sensitivity of these cells to apoptotic agents. This hints that p53 interacts with a functional BLM protein to initiate apoptosis. In fact, several DNA helicases, including BLM and WRN, were found to bind at the C-terminus of the p53 protein (11). A direct interaction between BLM and p53 may occur in nuclear bodies (NBs), as NBs are known to be involved in the regulation of apoptotic pathways. Experiments have shown that mutant BLM proteins were unable to congregate in NBs and hence disrupted p53-mediated apoptosis (11–13).

An experiment by Chester et al. demonstrated that BLM knockout mouse embryonic fibroblasts show a large burst of apoptosis early on in development, which gradually decreases with time. This could explain why individuals with BS experience a developmental delay when compared to their unaffected peers (14).

The surviving BS cells are thought to escape apoptosis by a primitive SOS-type mechanism (figure 3). In normal cells, it is common for replication forks to stall during DNA replication as they encounter a section of DNA damage. This "pause" in the replication process can be rectified with the aid of RecQ helicases, such as BLM in humans, and RecG helicase in bacteria. These proteins can recognise D-loops which form at stalled replication forks and resume the replication process by rectifying the error, without the need for chromosomal DNA breaks. If the required helicases are mutated and are unable to repair stalled replication forks, additional pathways may take over to allow the cell to escape apoptosis. This is the basis of the SOS-hypothesis and can be seen in primitive organisms like bacteria. This process involves creating chromosomal DNA breaks and the subsequent formation of D-loops. In the functional absence of certain helicases, the replication fork is restored through crossing over and genetic recombination. This mechanism explains why the BS cells that escaped apoptosis show increased chromosome breakages and hyper-recombination (15). The newly formed hyper-recombinant DNA shows a greater risk of unmasking recessive genes that can potentially cause harm, such as oncogenes. This can be achieved by either of the two mechanisms. In a heterozygous individual, a deletion of the dominant allele which is not replaced will result in hemizygosity for the recessive allele.

If the deleted dominant allele is replaced by a recessive one, the individual is rendered homozygous recessive (16).

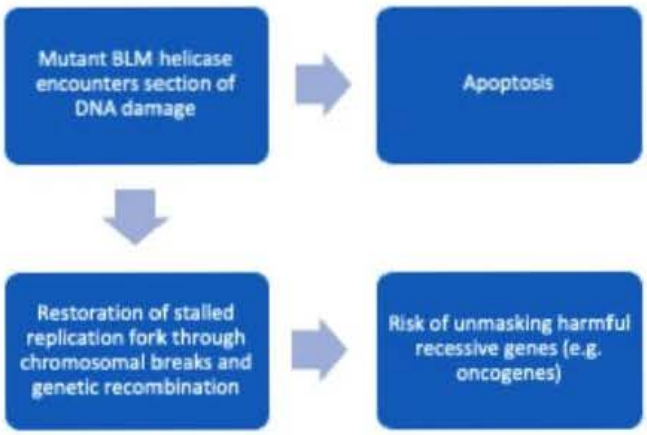

Figure 3: Flowchart showing molecular basis of BS pathogenesis

5. Other Complications

Many conditions can lead to children born SGA. While growth hormone (GH) is a popular treatment option, it is not advisable in BS and other chromosomal breakage syndromes. This is because BS patients are at an increased risk of developing neoplasms and GH treatment would encourage existing neoplasms to proliferate further. Hence, this poses a challenge for physicians treating SGA children whose disease aetiology is unknown. If an SGA child on GH treatment shows insulin-like growth factor 1 (IGF-1) levels above 2.5 Standard Deviation Score (SDS) and is showing little growth progress, one should consider checking for a mutation in the IGF1R gene.

This is because such mutations can render the individual insensitive to IGF-1. If no such mutations are present, BS and similar genetic conditions should be considered, especially if the parents of the individual are closely related (4).

As of yet, there is no cure for BS and symptomatic treatment must be tailored to the individual to avoid exacerbation of the condition. For example, chemotherapy is given at much lower doses than unaffected individuals and radiotherapy is avoided altogether. This is because BS cells lack appropriate DNA repair mechanisms, therefore DNA damage may lead to a more aggressive cancer or additional primary tumours (17).

6. Conclusion

Given these points, BS seems to be the result of evolutionary mechanisms that spare defective cells from death, resulting in various complications such as cancer, skin lesions, small size, and endocrine abnormalities (15). BS may be considered in screening programmes for populations at risk and should be considered as a potential diagnosis if SGA children not responding to GH treatment do not have an IGF1R mutation (4,6). Furthermore, a collaborative effort between medics, scientists and pharmaceutical companies is needed to raise awareness of rare diseases and to improve understanding of the underlying disease mechanisms with the hope of finding potential cures.

For this to take place, there needs to be strong patient participation, biobanking systems and curated rare disease databases (17).

References

1. Bloom D. Congenital Telangiectatic Erythema Resembling Lupus Erythematosus In Dwarfs Probably a Syndrome Entity. Arch Pediatr Adolesc Med. 1954 Dec 1;88(6):754.

2. German J. Bloom's syndrome. I. Genetical and clinical observations in the first twenty-seven patients. Am J Hum Genet. 1969 Mar;21(2):196–227.

3. German J. Bloom's syndrome. XX. The first 100 cancers. Cancer Genetics and Cytogenetics. 1997 Jan;93(1):100–6.

4. Renes JS, Willemsen RH, Wagner A, Finken MJJ, Hokken-Koelega ACS. Bloom Syndrome in Short Children Born Small for Gestational Age: A Challenging Diagnosis. The Journal of Clinical Endocrinology & Metabolism. 2013 Oct;98(10):3932–8.

5. Karow JK, Wu L, Hickson ID. RecQ family helicases: roles in cancer and aging. Current Opinion in Genetics & Development. 2000 Feb;10(1):32–8.

6. Li L, Eng C, Desnick RJ, German J, Ellis NA. Carrier Frequency of the Bloom Syndrome blmAsh Mutation in the Ashkenazi Jewish Population. Molecular Genetics and Metabolism. 1998 Aug;64(4):286–90.

7. German J, Sanz MM. Weill Cornell Medical Center | Bloom's Syndrome Registry [Internet]. 2009 [cited 2020 Sep 14]. Available from: http://pre.weill.cornell.edu/bsr/data_from_registry/

8. Chaganti RSK, Schonberg S, German J. A Manyfold Increase in Sister Chromatid Exchanges in Bloom's Syndrome Lymphocytes. Proceedings of the National Academy of Sciences. 1974 Nov 1;71(11):4508–12.

9. Sun H, Karow JK, Hickson ID, Maizels N. The Bloom's Syndrome Helicase Unwinds G4 DNA. J Biol Chem. 1998 Oct 16;273(42):27587–92.

10. Duguet M. When helicase and topoisomerase meet! J Cell Sci. 1997 Jun 15;110(12):1345.

11. Wang XW, Tseng A, Ellis NA, Spillare EA, Linke SP, Robles AI, et al. Functional Interaction of p53 and BLM DNA Helicase in Apoptosis. J Biol Chem. 2001 Aug 31;276(35):32948–55.

12. Zhong S, Hu P, Ye T-Z, Stan R, Ellis NA, Pandolfi PP. A role for PML and the nuclear body in genomic stability. Oncogene. 1999 Dec;18(56):7941–7.

13. Yankiwski V, Marciniak RA, Guarente L, Neff NF. Nuclear structure in normal and Bloom syndrome cells. Proceedings of the National Academy of Sciences. 2000 May 9;97(10):5214–9.

14. Chester N, Kuo F, Kozak C, O'Hara CD, Leder P. Stage-specific apoptosis, developmental delay, and embryonic lethality in mice homozygous for a targeted disruption in the murine Bloom's syndrome gene. Genes & Development. 1998 Nov 1;12(21):3382–93.

15. Amor-Guéret M. Bloom syndrome, genomic instability and cancer: the SOS-like hypothesis. Cancer Letters. 2006 May;236(1):1–12.

16. Bishop AJR, Schiestl RH. Role of homologous recombination in carcinogenesis. Experimental and Molecular Pathology. 2003 Apr;74(2):94–105.

17. Campbell MB, Campbell WC, Rogers J, Rogers N, Rogers Z, Hurk AM van den, et al. Bloom syndrome: research and data priorities for the development of precision medicine as identified by some affected families. Cold Spring Harb Mol Case Stud. 2018 Jan 4;4(2):a002816.

Author:
Katya Bartolo

Reviewers:
Dr. Ruben Cauchi
Dr. Christian Zammit

Spinocerebellar Ataxia Type 2 and its Association with Amyotrophic Lateral Sclerosis

Abstract

All the neurodegenerative diseases seem to have a few common patterns. Recent studies have discovered similarities between Amyotrophic Lateral Sclerosis (ALS) and a sub-type of the Spinocerebellar Ataxia (SCA) diseases. SCA is characterised by different sub-types; the sub-type Spinocerebellar Ataxia Type 2 (SCA2) is particularly related to ALS. Similarities in both diseases with other types of neurodegenerative diseases make it difficult to diagnose at onset and hence symptomatic treatment, not cure, is usually started later on in the progression of the disease.

In this article, a brief description of both diseases and an overview of the genetics of the individual diseases are outlined. In particular, reference is made to studies which have shown that the pathological number of CAG trinucleotide repeat-expansions in the ATXN2 gene are causative of SCA2 or even ALS.

Amyotrophic Lateral Sclerosis

ALS involves progressive motor neuron loss in the spinal cord and in the brain, affecting both lower motor neurons (LMNs) and upper motor neurons (UMNs). It is a neurodegenerative syndrome and not a neuromuscular disease, sharing pathobiological characteristics with frontotemporal dementia (FTD) (Van Es et al., 2017). ALS is a fatal type of motor neuron disorder (Zarei et al., 2015). Symptoms usually emerge in patients aged between 50 and 65 (Logroscino et al., 2009), however, young-onset ALS has been diagnosed and observed clinically (Artemiadis et al., 2016).

ALS can be divided into two forms:

- Familial ALS (FALS);
- Sporadic ALS (SALS).

The sporadic form is the most common form. 90%-95% of all cases reported are of the sporadic type. The sporadic form has no evident genetically acquired component.

The other type, FALS, represents the rest of the 5%-10% of cases (Ticozzi et al., 2011). The latter have a genetically dominant inheritance factor with 30 or more affected genes (Renton et al., 2013).

To date no one has developed a cure for ALS. Patients suffering from ALS more often than not, complain of fatigue, which may eventually cause distress and impair quality of life (QoL) (Gibbons et al., 2018).

Slowing down disease progression is the current aim of clinical trials. This is done by testing those drugs that work on the processes that come about after the onset of the disease. Current novel therapies that are in trial include (Gordon, 2011):

- Vaccine therapies;
- Injections of stem cells;
- Neuroprotective agents with different acting mechanisms; and
- Diaphragmatic pacing.

ALS patients have an approximate life expectancy of 3 years following onset of symptoms. In approximately 5% of patients, however, there is a range of survival between a few months and ten years or longer (Gordon, 2011). At the last stages of life the only available comfort to patients is palliative care.

Spinocerebellar Ataxia

SCAs are a subgroup of a group of autosomal dominant cerebellar ataxias which are hereditary. Ataxias and SCAs share the same clinical features. Cerebellar ataxias are the progressive type of neurodegenerative diseases affecting primarily the cerebellum with progressive degeneration but also affecting other regions which are connected, including the brainstem.

CAG repeat expansions coding for polyglutamine are observed in many SCAs suggesting that the disease involves the polyglutamine protein (polyQ), which is the toxic type (Sullivan et al., 2018).

The disease is mostly adult onset (Klockgether et al., 2019). In particular, SCA type 2 is caused by CAG nucleotide repeat expansions in the gene ATXN2, which codes for the ataxin-2 protein. Patients with this disease present with slow saccades and progressive ataxia (Scoles & Pulst, 2018).

To date no treatment to stop or slow SCAs has been found, many of which terminate in premature death. Patients suffering from SCA receive clinical care which manages the disease's symptoms.

Genetics of ALS

In approximately 60% to 80% of FALS patients, mutations of genes of grand effect are identified, in particular, mutations in the below tabulated genes (Renton et al., 2013):

Genes:	Percentage of patients:
Chromosome 9 open reading frame 72 (C9orf72)	40%
Superoxide dismutase 1 (SOD1)	20%
Fused in Sarcoma (FUS)	1.5%
TARDBP-43 (Trans-active response DNA-binding protein 43 [TDP-43])	1.5%

Table 1: Patient Percentages of Gene Mutations in FALS. Most patients (40%) with FALS present with a gene mutation in C9orf72. Second most common mutation (20%) is in the SOD1 gene, followed by roughly equal lesser presentations (1.5%) of FUS and TDP-43 gene mutations.

The inheritance in FALS patients follows a Mendelian genetic pattern and is autosomal dominant (He et al., 2014). The C9orf72 gene mutation in FALS is referred to as a hexanucleotide repeat expansion (HRE). This mutation causes degeneration of neurons in 3 ways (Brown & Al-Chalabi, 2017; Balendra & Isaacs, 2018):

- Loss of function;
- Ribonucleic acid (RNA) toxicity - which leads to toxic gain of function; and
- Dipeptide repeat proteins (DRPs) – which also lead to toxic gain of function.

Mutations in the SOD1 gene cause cell cytotoxicity. It primarily affects RNA and deoxyribonucleic acid (DNA) metabolism.

Adenosine triphosphate (ATP) production and free calcium release in the mitochondria are also impacted. Astrocytes and microglia that are associated with motor neurons are also impaired and hence cause progression of the ALS disease. This disease progression is caused because of the astrocyte cells' reduced uptake of glutamate resulting in the accumulation of glutamate - which is toxic to the motor neurons (Pasinelli & Brown, 2006).

Both FUS and TDP-43 are genes which are responsible for gene regulation and gene expression. In particular, RNA splicing, transcription, translation, transport and the processing of regulatory RNA (Kiernan et al., 2011).

Genetics of SCA2

SCAs are genetically grouped according to repeat expansions. In most SCAs, damage is caused to the Purkinje neurons in the cerebellum which results in atrophy of the cerebellum. The damage is not only limited to the cerebellum, however, damage may also be caused to the brainstem pontine nuclei, basal ganglia and the spinal cord (Klockgether et al., 2019).

In particular, SCA2 disease is caused by a trinucleotide CAG expansion of 31 or more repeats in the gene that codes for the ataxin-2 protein, i.e. ATXN2. The trinucleotide repetitive sequence of (CAG)8(CAA)1(CAG)4(CAA)1(CAG)8 found in the amino-terminus of the gene codes for repetitive glutamine residues. CAA trinucleotides also code for glutamine, however, their presence in the repetitive sequence allows for stability of the expansion and has an effect on the secondary structure of RNA (Sobczak & Krzyzosiak, 2005). These observations are said to possibly contribute to the disease's phenotypic variability (Antenora et al., 2017).

Ataxin-2 in ALS and SCA

The ataxin-2 protein is expressed in normal human brain, in particular, in the midbrain, trochlear neurons, Purkinje neurons and large neurons found in the substantia nigra. Wild-type protein ataxin-2 is limited to the cytoplasm, but it can also be found in the endoplasmic reticulum and Golgi apparatus (van de Loo et al., 2009). The pattern of ataxin-2 expression was the same both in the brains of SCA2 patients and in unaffected individuals (Antenora et al., 2017).

The exact function of ataxin-2 is still not known. A study conducted on mice deficient of ataxin-2 showed that they remained viable and only gained weight when fed on a fat-enhanced diet, indicating that its function in development is not essential (Kiehl et al., 2006). Other studies showed evidence that it is involved in the regulation of the amount of calcium released from endoplasmic reticula, involved in RNA processing and also in stress granules assembly as well as epidermal growth factor receptor (EGFR) endocytic trafficking (Antenora et al., 2017).

Alleles are said to be 'normal' if they have CAG repeats in the ATXN2 gene which amount to 31 or even lower. SCA2 is seen in patients with an expansion of CAG repeats in the ataxin-2 gene. A CAG repeat expansion in the ATXN2 gene greater than or equal to 34 is causative of SCA2 (Pulst et al., 1996).

Elden et al., (2010) suggested that 29 to 34 repeat expansions of the trinucleotide CAG repeats at the ATXN2 polyQ locus present a risk factor for ALS. This type of ATXN2-associated ALS is referred to as classic ALS because it presents with a number of UMN and

LMN signs. In this particular type of ALS it is reported that in the cerebellar vermis there is remarked loss of Purkinje cerebellar cells which is not present in other forms of ALS (Tan et al., 2016).

This link is in line with the study that many risk genes in ALS, in particular TDP-43 are involved in RNA metabolism hence further enhancing the observed link between the proteins ataxin-2 and TDP-43. TDP-43, like ataxin-2, is involved in certain RNA processes especially in RNA stability, alternative splicing and transcription all of which are associated with RNA metabolism (Paulson et al., 2017).

In a study using a yeast screen, the Pab1p-binding protein (PBP1), which is a yeast homologue of ataxin-2, is shown to increase toxicity which is TDP-43 mediated. This increase in TDP-43 toxicity was also related to the ATX-2 Drosophila homolog of ataxin-2. This concludes that the association between ataxin-2 and TDP-43 is RNA-dependent in both mammalian and yeast cells (Elden et al., 2010). It was also observed that ataxin-2, like TDP-43 is mis-localised to the cytoplasm in motor neurons of ALS patients giving it a toxic gain-of-function. The trinucleotide CAG intermediate-length repeat expansions were observed to be less frequent in normal individuals as opposed to ALS patients (Van Damme et al., 2011). This concludes that the polyQ length in the ATXN2 gene (wild-type as well) affects the function in RNA metabolism, involving both ataxin-2 and TDP-43 (Paulson et al., 2017).

Community Care and Patient Well Being

In Malta, 'Dar Bjorn' is a nursing home for patients suffering from ALS and other neurological conditions. Ever since its setting up in November 2017, it has provided continuous aid and care for the residents of the nursing home.

It has helped in improving the QoL of patients suffering from neurological conditions, many of whom would not have had the same level of comfort from home.

Conclusion

Studies are being done on families to see if there are any families with coexisting ALS and SCA2. A study done by Tazen et al., (2013) showed how two members of the same family, a paternal uncle and his niece, were diagnosed with ALS and SCA2 respectively, both having the full CAG trinucleotide repeat expansion. Their family pedigree is shown in Figure 1. This study showed that the mutation in the ATXN2 gene can present with different phenotypes in the same family, hence strongly suggesting that genetic tests to check for polyQ repeat expansions in the ATXN2 gene should be done in patients suffering from ataxia and coming from an ALS family history.

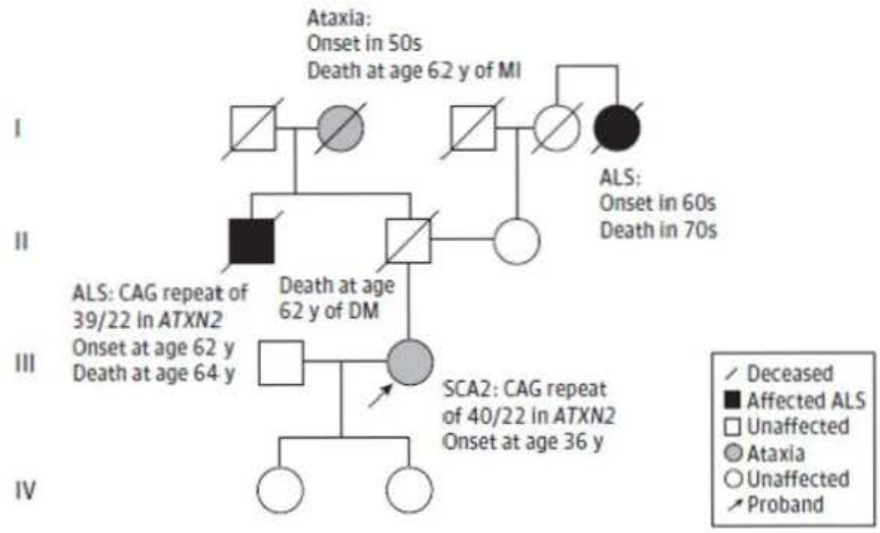

Figure 1:
Family Pedigree (Tazen et al., 2013). The proband – female with SCA2 with an unaffected mother and a deceased unaffected father, having CAG repeat expansions in ATXN2 . The paternal deceased uncle had ALS with the same trinucleotide repeat expansion as the proband but with different lengths.

References

1. Antenora A, Rinaldi C, Roca A, Pane C, Lieto M, Saccà F, Peluso S, De Michele G & Filla A (2017). The Multiple Faces of Spinocerebellar Ataxia type 2. Annals of Clinical and Translational Neurology 4, 687-695.

2. Artemiadis A, Peppas C, Giannopoulos S, Zouvelou V & Triantafyllou N (2016). Case of Young-Onset Sporadic Amyotrophic Lateral Sclerosis. Journal of Clinical Neuromuscular Disease 17, 220-222.

3. Balendra R & Isaacs A (2018). C9orf72-mediated ALS and FTD: multiple pathways to disease. Nature Reviews Neurology 14, 544-558.

4. Brown R & Al-Chalabi A (2017). Amyotrophic Lateral Sclerosis. New England Journal of Medicine 377, 162-172.

5. Elden A et al. (2010). Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS. Nature 466, 1069-1075.

6. Gibbons C, Pagnini F, Friede T & Young C (2018). Treatment of fatigue in amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database of Systematic Reviews; DOI: 10.1002/14651858.cd011005.pub2.

7. Gordon P (2011). Amyotrophic Lateral Sclerosis. CNS Drugs 25, 1-15.

8. He J, Mangelsdorf M, Fan D, Bartlett P & Brown M (2014). Amyotrophic Lateral Sclerosis Genetic Studies. The Neuroscientist 21, 599-615.

9. Kiehl T, Nechiporuk A, Figueroa K, Keating M, Huynh D & Pulst S (2006). Generation and characterization of Sca2 (ataxin-2) knockout mice. Biochemical and Biophysical Research Communications 339, 17-24.

10. Kiernan M, Vucic S, Cheah B, Turner M, Eisen A, Hardiman O, Burrell J & Zoing M (2011). Amyotrophic lateral sclerosis. The Lancet 377, 942-955.

11. Klockgether T, Mariotti C & Paulson H (2019). Spinocerebellar ataxia. Nature Reviews Disease Primers; DOI: 10.1038/s41572-019-0074-3.

12. Logroscino G, Traynor B, Hardiman O, Chio A, Mitchell D, Swingler R, Millul A, Benn E & Beghi E (2009). Incidence of amyotrophic lateral sclerosis in Europe. Journal of Neurology, Neurosurgery & Psychiatry 81, 385-390.

13. Pasinelli P & Brown R (2006). Molecular biology of amyotrophic lateral sclerosis: insights from genetics. Nature Reviews Neuroscience 7, 710-723.

14. Paulson H, Shakkottai V, Clark H & Orr H (2017). Polyglutamine spinocerebellar ataxias — from genes to potential treatments. Nature Reviews Neuroscience 18, 613-626.

15. Pulst S, Nechiporuk A, Nechiporuk T, Gispert S, Chen X, Lopes-Cendes I, Pearlman S, Starkman S, Orozco-Diaz G, Lunkes A, DeJong P, Rouleau G, Auburger G, Korenberg J, Figueroa C & Sahba S (1996). Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. Nature Genetics 14, 269-276.

16. Renton A, Chiò A & Traynor B (2013). State of play in amyotrophic lateral sclerosis genetics. Nature Neuroscience 17, 17-23.

17. Scoles D & Pulst S (2018). Spinocerebellar Ataxia Type 2. Polyglutamine Disorders 175-195.

18. Sobczak K & Krzyzosiak W (2005). CAG Repeats Containing CAA Interruptions Form Branched Hairpin Structures in Spinocerebellar Ataxia Type 2 Transcripts. Journal of Biological Chemistry 280, 3898-3910.

19. Sullivan R, Yau W, O'Connor E & Houlden H (2018). Spinocerebellar ataxia: an update. Journal of Neurology 266, 533-544.

20. Tan R, Kril J, McGinley C, Hassani M, Masuda-Suzukake M, Hasegawa M, Mito R, Kiernan M & Halliday G (2016). Cerebellar neuronal loss in amyotrophic lateral sclerosis cases with ATXN2 intermediate repeat expansions. Annals of Neurology 79, 295-305.

21. Tazen S, Figueroa K, Kwan J, Goldman J, Hunt A, Sampson J, Gutmann L, Pulst S, Mitsumoto H & Kuo S (2013). Amyotrophic Lateral Sclerosis and Spinocerebellar Ataxia Type 2 in a Family With Full CAG Repeat Expansions ofATXN2. JAMA Neurology; DOI: 10.1001/jamaneurol.2013.443.

22. Ticozzi N, Vance C, LeClerc A, Keagle P, Glass J, McKenna-Yasek D, Sapp P, Silani V, Bosco D, Shaw C, Brown R & Landers J (2011). Mutational analysis reveals the FUS homolog TAF15 as a candidate gene for familial amyotrophic lateral sclerosis. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 156, 285-290.

23. Van Damme P, Veldink J, van Blitterswijk M, Corveleyn A, van Vught P, Thijs V, Dubois B, Matthijs G, van den Berg L & Robberecht W (2011). Expanded ATXN2 CAG repeat size in ALS identifies genetic overlap between ALS and SCA2. Neurology 76, 2066-2072.

24. Van de Loo S, Eich F, Nonis D, Auburger G & Nowock J (2009). Ataxin-2 associates with rough endoplasmic reticulum. Experimental Neurology 215, 110-118.

25. Van Es M, Hardiman O, Chio A, Al-Chalabi A, Pasterkamp R, Veldink J & van den Berg L (2017). Amyotrophic lateral sclerosis. The Lancet 390, 2084-2098

.

26. Zarei S, Carr K, Reiley L, Diaz K, Guerra O, Altamirano P, Pagani W, Lodin D, Orozco G & Chinea A (2015). A comprehensive review of amyotrophic lateral sclerosis. Surgical Neurology International 6, 171.

Authors:
Deborah Caruana &
Jennifer Xuereb

Reviewers:
Dr. Christian Zammit
Prof. Josanne Vassallo

Neonatal Hypoglycaemia: A Review

Introduction

The brain accounts for 20-25% of the total body glucose metabolism (1),(2). The brain is dependent on a continuous supply of glucose transported by the blood, since the endogenous levels of glucose in the brain are not sufficient (3),(4). When the metabolic demand supersedes the availability of glucose, hypoglycemia ensues, which leads to neuronal injury and ultimately may even result in hypoglycaemic coma and death (5). Maintaining a plasma glucose level of 4-6mmol/L is essential for human survival, especially when concerning the brain. Hypoglycemia is achieved when these values decrease to 3mmol/l or lower (6,7). Moreover, the most common metabolic problem in the newborn is neonatal hypoglycaemia, occurring in 19% of neonates (8–12).

Neonatal Hypoglycaemia

Neonatal hypoglycaemia may be classified into two categories. The most common type is short-term transient hypoglycemia, which occurs approximately 1-12 hours after delivery. It usually presents as the incapability to maintain normal blood glucose levels during the transition from intrauterine to extrauterine life. (13) At birth, the glucose concentration of the neonate is approximately 70% of that of the mother. After an hour, the neonatal glucose levels fall abruptly to an all-time low at around 1.11-1.39mmol/l. (14) This fall is usually seen in healthy neonates, as these low levels are considered to be temporary.

Moreover, they should start to rise in the first few hours and days after delivery.

This is an expected adjustment of postnatal life so as to maintain glucose homeostasis. (14–16) The abrupt fall in glucose is essential to promote the production of glucose through the processes of glycogenolysis and gluconeogenesis. In addition, this also stimulates appetite in the neonate helping in the adaptation of the feeding cycles. (17)

On the other hand, the rarer type of hypoglycaemia is known as persistent hypoglycemia, which is harder to treat. This results in recurrent low blood

glucose and hence requiring high glucose transfusion rates.

Moreover, it is commonly found in patients having disorders of hormone excess such as hyperinsulinism which causes an excessive production of insulin. It may also be caused by a lack of glycogen stores, inefficient glucose production and also the inability to synthesize glucose. (13)

Causes of Neonatal Hypoglycaemia

The mechanism of transient hypoglycaemia is still not fully understood, however, some cases may be due to mutations in genes that modulate β-cells' secretion of insulin. This is usually referred to as monogenic congenital hyperinsulinism, which gives rise to hypoglycemia. (18,19) In fact, in severe and persistent hyperinsulinaemic hypoglycaemia, over half of the patients have a known underlying genetic basis which demonstrates dysregulation of insulin secretion. (20–23)

Preterm babies and neonates which experience intrauterine growth restriction have decreased glycogen stores and overall adipose tissues. Since they typically tend to be smaller and have a lower birth weight (lower than 1000g), they have a comparatively larger brain size which has high metabolic demands. Moreover, it is found that preterm infants tend to have low enzymes which are utilized in gluconeogenesis. (24) Hence, overall they are incapable of producing enough amounts of endogenous glucose which as a result puts them at higher risk of hypoglycemia.

Diabetic mothers and larger infants are at risk of experiencing foetal hyperinsulinism and a higher level of utilization of peripheral glucose which is what puts them at risk of hypoglycemia. This occurs due to the fact that when in utero, the maternal glucose concentration levels greatly impact that of the foetus since glucose is transferred directly from the mother via the placenta. Hence, if there is a prolonged elevation in the maternal glucose, the fetus will experience hyperglycemia and overstimulation of the pancreas to produce higher insulin levels. High fetal insulin levels tend to linger after birth and since the neonate no longer can depend on the sustained source of glucose from the mother, their blood glucose concentration will decline significantly due to the abnormally rapid rate of utilization of glucose. (24)

In the case of infants undergoing perinatal stress such as: perinatal ischemia, maternal eclampsia / preeclampsia, sepsis, hypothermia and congenital heart disease there is an increase in the metabolic utilization of glucose, hence contributing to a state called hypoglycaemic hyperinsulinism. (24–27)

Complications

Prolonged blood glucose levels lower than 2.2mmol/L may be potentially neuroglycopenic. (13) Moreover, this condition could result in cerebral injury including; cerebral cortical atrophy, parenchymal hemorrhage, white matter injury and ischemic stroke. (28–33) Additionally it may also result in various adverse neurologic outcomes such as cerebral palsy, blindness, epilepsy and intellectual disability. (28,32,34–40) Infants suffering from persistent hyperinsulinemic hypoglycaemia develop severe neural damage, since it is believed that isolated hypoglycaemia without any other contributing factors enhances hypoxic-ischaemic brain injury. Hence, treatment to aid the maintenance of glucose in the brain is detrimental. (36,41)

Despite the reason being unclear, it shows that during neonatal hypoglycemia, there is often occipital and parietal lobe involvement. (28,30,42) Some authors have said that the main reason could be due to having a higher demand for glucose to be utilised for extensive growth of axons. On the other hand, it was also suggested that this could be attributed to the excitatory neurotransmitters which are found in various areas of the brain. (30,40,42) Apart from these regions the corpus callosum, corticospinal tracts, deep gray nuclei and the remaining cerebral hemisphere may also be affected by hypoglycaemia. (28,30,42,43)

Prevention

There are various strategies for preventing neonatal hypoglycaemia. Firstly, high-risk infants are screened so that immediate care may be provided. Furthermore, it is of utmost importance to identify the cause of hypoglycaemia and to make sure it is transient and not persistent. Currently, one of the preventive measures used for infants who are at risk is regular milk feedings using breast milk or formula milk. Glucose water feedings are no longer administered, as this method is unable to support gluconeogenesis due to the fact that it does not provide the neonate with carbohydrate, fat and protein as opposed to milk feedings. (44–46)

Conclusion

Despite all the research done on neonatal hypoglycaemia, the ideal treatment strategy is still riddled with uncertainty, especially when considering neonates which present with asymptomatic hypoglycemia. There are various recommendations from different organizations with the role of helping clinicians deal with neonates born with low glucose levels. The American Academy of Paediatrics guidelines address the first 24-28hrs while the Pediatric Endocrine Society recommendations aid to differentiate between physiological low levels of glucose from those that persist beyond 48hrs of life. (13,25) The variance in expert opinions reflects the need for more research on this area of study.

References

1. Mink JW, Blumenschine RJ, Adams DB. Ratio of central nervous system to body metabolism in vertebrates: its constancy and functional basis. Am J Physiol. 1981 Sep;241(3):R203-12.

2. Raichle ME, Posner JB, Plum F. Cerebral blood flow during and after hyperventilation. Arch Neurol. 1970 Nov;23(5):394–403.

3. Nehlig A. Cerebral energy metabolism, glucose transport and blood flow: changes with maturation and adaptation to hypoglycaemia. Diabetes Metab. 1997 Feb;23(1):18–29.

4. Siesjö BK. Hypoglycemia, brain metabolism, and brain damage. Diabetes Metab Rev. 1988 Mar;4(2):113–44.

5. Yu Y, Herman P, Rothman DL, Agarwal D, Hyder F. Evaluating the gray and white matter energy budgets of human brain function. J Cereb Blood Flow Metab. 2018;38(8):1339–53.

6. Gonder-Frederick LA, Cox DJ, Driesen NR, Ryan CM, Clarke WL. Individual differences in neurobehavioral disruption during mild and moderate hypoglycemia in adults with IDDM. Diabetes. 1994 Dec;43(12):1407–12.

7. Zammitt NN, Warren RE, Deary IJ, Frier BM. Delayed recovery of cognitive function following hypoglycemia in adults with type 1 diabetes: effect of impaired awareness of hypoglycemia. Diabetes. 2008 Mar;57(3):732–6.

8. Cornblath M, Hawdon JM, Williams AF, Aynsley-Green A, Ward-Platt MP, Schwartz R, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. Pediatrics. 2000 May;105(5):1141–5.

9. Hegarty JE, Harding JE, Crowther CA, Brown J, Alsweiler J. Oral dextrose gel to prevent hypoglycaemia in at-risk neonates. Cochrane Database Syst Rev. 2017 Jul 24;

10. Hussain K, Chandran S, Rajadurai V, Alim A. Current perspectives on neonatal hypoglycemia, its management, and cerebral injury risk. RRN. 2015 Feb;17.

11. Hay WW, Raju TN, Higgins RD, Kalhan SC, Devaskar SU. Knowledge gaps and research needs for understanding and treating neonatal hypoglycemia: workshop report from Eunice Kennedy Shriver National Institute of Child Health and Human Development. J Pediatr. 2009 Nov;155(5):612–7.

12. Kaiser JR, Bai S, Gibson N, Holland G, Lin TM, Swearingen CJ, et al. Association Between Transient Newborn Hypoglycemia and Fourth-Grade Achievement Test Proficiency: A Population-Based Study. JAMA Pediatr. 2015 Oct;169(10):913–21.

13. Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr. 2015 Aug;167(2):238–45.

14. Srinivasan G, Pildes RS, Cattamanchi G, Voora S, Lilien LD. Plasma glucose values in normal neonates: a new look. J Pediatr. 1986 Jul;109(1):114–7.

15. Heck LJ, Erenberg A. Serum glucose levels in term neonates during the first 48 hours of life. J Pediatr. 1987 Jan;110(1):119–22.

16. Rozance PJ. Update on neonatal hypoglycemia. Curr Opin Endocrinol Diabetes Obes. 2014 Feb;21(1):45–50.

17. Rozance PJ, Hay WW. Neonatal hypoglycemia—answers, but more questions. J Pediatr. 2012 Nov;161(5):775–6.

18. Shah P, Rahman SA, Demirbilek H, Güemes M, Hussain K. Hyperinsulinaemic hypoglycaemia in children and adults. Lancet Diabetes Endocrinol. 2017;5(9):729–42.

19. Stanley CA. Perspective on the genetics and diagnosis of congenital hyperinsulinism disorders. J Clin Endocrinol Metab. 2016 Mar;101(3):815–26.

20. Thomas PM, Cote GJ, Wohllk N, Haddad B, Mathew PM, Rabl W, et al. Mutations in the sulfonylurea receptor gene in familial persistent hyperinsulinemic hypoglycemia of infancy. Science. 1995 Apr 21;268(5209):426–9.

21. Vredendaal PJ, van den Berg IE, Malingré HE, Stroobants AK, Olde Weghuis DE, Berger R. Human short-chain L-3-hydroxyacyl-CoA dehydrogenase: cloning and characterization of the coding sequence. Biochem Biophys Res Commun. 1996 Jun 25;223(3):718–23.

22. Clayton PT, Eaton S, Aynsley-Green A, Edginton M, Hussain K, Krywawych S, et al. Hyperinsulinism in short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency reveals the importance of β-oxidation in insulin secretion. J Clin Invest. 2001 Aug 1;108(3):457–65.

23. Li C, Chen P, Palladino A, Narayan S, Russell LK, Sayed S, et al. Mechanism of hyperinsulinism in short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency involves activation of glutamate dehydrogenase. J Biol Chem. 2010 Oct 8;285(41):31806–18.

24. Sharma A, Davis A, Shekhawat PS. Hypoglycemia in the preterm neonate: etiopathogenesis, diagnosis, management and long-term outcomes. Transl Pediatr. 2017 Oct;6(4):335–48.

25. Committee on Fetus and Newborn, Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics. 2011 Mar;127(3):575–9.

26. Tin W. Defining neonatal hypoglycaemia: a continuing debate. Semin Fetal Neonatal Med. 2014 Feb;19(1):27–32.

27. Harris DL, Battin MR, Weston PJ, Harding JE. Continuous glucose monitoring in newborn babies at risk of hypoglycemia. J Pediatr. 2010 Aug;157(2):198-202.e1.

28. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics. 2008 Jul;122(1):65–74.

29. Aslan Y, Dinc H. MR findings of neonatal hypoglycemia. AJNR Am J Neuroradiol. 1997 May;18(5):994–6.

30. Barkovich AJ, Ali FA, Rowley HA, Bass N. Imaging patterns of neonatal hypoglycemia. AJNR Am J Neuroradiol. 1998 Mar;19(3):523–8.

31. Murakami Y, Yamashita Y, Matsuishi T, Utsunomiya H, Okudera T, Hashimoto T. Cranial MRI of neurologically impaired children suffering from neonatal hypoglycaemia. Pediatr Radiol. 1999 Jan;29(1):23–7.

32. Filan PM, Inder TE, Cameron FJ, Kean MJ, Hunt RW. Neonatal hypoglycemia and occipital cerebral injury. J Pediatr. 2006 Apr;148(4):552–5.

33. Yalnizoglu D, Haliloglu G, Turanli G, Cila A, Topcu M. Neurologic outcome in patients with MRI pattern of damage typical for neonatal hypoglycemia. Brain Dev. 2007 Jun;29(5):285–92.

34. Boardman JP, Wusthoff CJ, Cowan FM. Hypoglycaemia and neonatal brain injury. Arch Dis Child Educ Pract Ed. 2013 Feb;98(1):2–6.

35. Arhan E, Öztürk Z, Serdaroğlu A, Aydın K, Hirfanoğlu T, Akbaş Y. Neonatal hypoglycemia: A wide range of electroclinical manifestations and seizure outcomes. Eur J Paediatr Neurol. 2017 Sep;21(5):738–44.

36. Menni F, de Lonlay P, Sevin C, Touati G, Peigné C, Barbier V, et al. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. Pediatrics. 2001 Mar;107(3):476–9.

37. Udani V, Munot P, Ursekar M, Gupta S. Neonatal hypoglycemic brain - injury a common cause of infantile onset remote symptomatic epilepsy. Indian Pediatr. 2009 Feb;46(2):127–32.

38. Montassir H, Maegaki Y, Ohno K, Ogura K. Long term prognosis of symptomatic occipital lobe epilepsy secondary to neonatal hypoglycemia. Epilepsy Res. 2010 Feb;88(2–3):93–9.

39. Tam EWY, Widjaja E, Blaser SI, Macgregor DL, Satodia P, Moore AM. Occipital lobe injury and cortical visual outcomes after neonatal hypoglycemia. Pediatrics. 2008 Sep;122(3):507–12.

40. Karimzadeh P, Tabarestani S, Ghofrani M. Hypoglycemia-occipital syndrome: a specific neurologic syndrome following neonatal hypoglycemia? J Child Neurol. 2011 Feb;26(2):152–9.

41. Volpe JJ. Hypoglycemia and brain injury. Neurology of the newborn. Elsevier; 2008. p. 591–618.

42. Alkalay AL, Flores-Sarnat L, Sarnat HB, Moser FG, Simmons CF. Brain imaging findings in neonatal hypoglycemia: case report and review of 23 cases. Clin Pediatr (Phila). 2005 Dec;44(9):783–90.

43. Tam EWY, Haeusslein LA, Bonifacio SL, Glass HC, Rogers EE, Jeremy RJ, et al. Hypoglycemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in neonates at risk for encephalopathy. J Pediatr. 2012 Jul;161(1):88–93.

44. Wight N, Marinelli KA, Academy of Breastfeeding Medicine. ABM clinical protocol #1: guidelines for blood glucose monitoring and treatment of hypoglycemia in term and late-preterm neonates, revised 2014. Breastfeed Med. 2014 May;9(4):173–9.

45. Cordero L, Ramesh S, Hillier K, Giannone PJ, Nankervis CA. Early feeding and neonatal hypoglycemia in infants of diabetic mothers. SAGE Open Med. 2013 Dec 19;1:2050312113516613.

46. Harris DL, Gamble GD, Weston PJ, Harding JE. What happens to blood glucose concentrations after oral treatment for neonatal hypoglycemia? J Pediatr. 2017 Jul 11;190:136–41.

Authors:
Rachel Anne Muscat Baron &
Abigail Micallef

Reviewers:
Dr. Edith Said
Prof. Charles Savona Ventura

The Pathophysiology of Hydrops Fetalis

Introduction

Hydrops fetalis (HF) is a condition that develops during foetal life. It is defined as the abnormal accumulation of fluid in at least two serous cavities and/or within the soft tissues of the foetus. This includes ascites, pericardial effusion, skin oedema and pleural effusion (1,2).

Studies have shown that the current incidence of HF is 1.80 per 1,000 total births with a mortality rate as high as 50% to this day, despite the advancements made in foetal intervention and neonatal care (3–5)

There are two main causes of HF, immune and non-immune. The immune cause of HF was previously the major cause of HF, however, due to the introduction of preventative medicine, there has been a marked reduction of cases in the western world, which have now been surpassed by the non-immune causes (6),(7,8).

Immune causes are due to antigen-antibody incompatibility of the mother and the developing foetus, leading to maternal immunological response to the paternally inherited antigens of the foetus (9). Non-immune causes include cardiovascular disorders, lymphatic dysplasias, haematological abnormalities, chromosomal imbalances, infections, conditions during pregnancy, metabolic disorders, tumours, and idiopathic ones. The pathophysiology leading to non-immune hydrops fetalis (NIHF) hence, depends on the cause.

List of Abbreviations

cGMP	Cyclic guanosine monophosphate
HF	Hydrops Fetalis
IHF	Immune hydrops fetalis
NIHF	Non-immune hydrops fetalis
RBCs	Red Blood Cells

Transport of Foetal Fluids

The foetus has a high risk of fluid accumulation due to the physiology of the microcirculatory and lymphatic system during development (10). Both the capillary filtration coefficient and reflection coefficient, as in the Starling Principle, imply that the endothelium is an important structure in determining the net movement of fluid between the different compartments (10). Damage to the glycocalyx makes the capillary endothelium more permeable (11,12). In such a case, due to a smaller driving force, water retains in interstitial space resulting in NIHF. Presence of high glucose level brings an increase in metabolic rate, which without rising levels of oxygen results in foetal hypoxia, acidosis, as well as, severe accumulation of fluid (11).

Lymphatic Return

The lymphatic system regulates the return of solutes and extracellular fluid to the circulation, and functions in immune cell trafficking (13). This can occur after the sixth embryonic week, once lymphangiogenesis has taken place (14). The rate of fluid extravasation and lymphatic return must be approximately equal, otherwise, a decline in lymphatic return leaves foetal oedema due to interstitial space expansion, and eventually hydrops (11,15). HF can also develop in cases of drastic reduction in lymphatic flow due to rise in foetal venous pressure (11).

Foetal Transmission to Amniotic Fluid

Amniotic fluid is the product of foetal skin transudation made approximately from the tenth to the twentieth week, such that its composition is similar to that of the foetal extracellular fluid (11,16). During this time, keratinisation of foetal membranes has not yet occurred hence, water and solute transport can occur by diffusion. The syncytiotrophoblast and the placental villi contain aquaporin 4, contributing to water transport into the amniotic sac too (17). NIHF can therefore also develop from the incorrect function of these aquaporins (11).

In the second half of pregnancy, amniotic fluid is synthesised by the lungs and urine of the foetus (11),(16). Placental or renal malfunctions therefore, likely change the fluid balance of the foetus and cause NIHF (11).

Isoimmunisation

Isoimmunisation is the process whereby antibodies form against antigens which are incompatible with those of another individual (7,8). This process may lead to the development of IHF, previously the major cause of HF, however, due to advancements in preventative medicine, this has been narrowed down to less than 10% of all HF etiologies (5), (6),(7,8).

The most common form is that of Rh incompatibility which occurs when the blood of negative Rh mothers is exposed to the positive Rh factor present in the developing foetus who would have inherited the positive Rh factor from the father (7,8),(18).

Rhesus factor is an antigen, which is a protein found on the cell surface membrane of red blood cells (RBCs). It is essential to determine whether the father is homozygous or heterozygous for the antigen to analyse the risk the foetus has in developing the haemolytic disease of the foetus (7,9,18)). Being that the inheritance of the positive factor is dominant, although the mother is negative for the antigen, the offspring could inherit the factor from the heterozygous or homozygous father (7,9,18).

Destruction of the placental barrier will cause fetomaternal haemorrhage which allows foetal blood to enter the maternal circulation (7,9,18)). Once the foreign antigens gain entry into the maternal circulation, they are able to incite the reticuloendothelial system reaction which identifies the foreign antigen and presents the antigens to the humoral immune system. The specialised B lymphocytes forming part of the humoral system recognises the antigen and mounts an immune response against these cells by synthesising IgM and IgG antibodies (7,9,18).

The initial response of the maternal immune system results in the formation of a low level of IgM antibodies. During the first pregnancy, the level tends to be insignificant and is unlikely to have an effect on the foetus as the humoral immune system requires time to elicit an effective antibody response (7,9).

The IgM antibodies are themselves too large to cross the placental barrier, however, they are able to form IgG antibodies that are smaller and able to cross (7,9,18). Hence, during the following Rh-D positive pregnancy, due to re-exposure to the antigen, the primary memory B cells made against these antigens will increase the IgG antibodies synthesised, the booster response. The IgG antibodies will cross the placenta by binding to the Fcy receptors of the syncytiotrophoblasts (7,9). The RBC-antibody bound cells are trapped within the foetal spleen and consequently destroyed by macrophages (7,9).

Endothelial Involvement

Studies have shown that the foetal plasma of alloimmunized pregnancies would have a decreased amount of cyclic guanosine monophosphate (cGMP), which is complicated by hydrops fetalis. The decrease in cGMP leads to damage of the foetal vascular endothelial cells, which thus leads to a decreased nitric oxide production by the

endothelial cells. This decrease can cause severe endothelial cell injury which is thought to lead to the development of ascites and oedema (19).

Foetal Anaemia

One of the major complications caused by Rh incompatibility is haemolysis. The decreased number of RBCs caused by haemolysis may result in hyperbilirubinemia or/and anaemia, therefore affecting morbidity and mortality (20,21). Ultrasonographically, this is noted by hepatosplenomegaly as well as pleural effusion, pericardial effusion, ascites, subcutaneous and scalp oedema. Furthermore, due to the decreased oxygen supply to the cells, placentomegaly may result, as a compensatory mechanism (7).

Circulation in the Foetus

Many of the congenital cardiac anomalies and disorders existing, change the flow volume of blood in the outflow tract and are the leading cause of cardiogenic NIHF (11,22). Owing to the ductus arteriosus, blood can pass from the pulmonary trunk to the aortic isthmus. Obstruction to this patent blood vessel can occur due to low partial pressure of oxygen, local nitric oxide production and high prostaglandin concentration, all of which reduce its patency (11,23).

In Due to resultant low oxygen levels of blood in the pulmonary circulation, pulmonary vessels constrict and increase their myogenic tone. This enhances the pulmonary vascular resistance, preventing rise in pulmonary artery pressure and inhibiting increase in blood flow at the left atrium (11,22).

turn, these maintain the foramen ovale patent, such that at diastole, blood flows from the right to the left side of the heart, rather than entering the pulmonary circulation. Simultaneously, abnormal left atrial pressure and a narrow foramen ovale decrease blood entering the left ventricle (22). This develops decreased ventricular compliance and hence, high end-diastolic volume and congestive heart failure. A high afterload also results in a small cardiac output. Resultant increase in pulmonary blood flow induces pulmonary lymphoedema, and this complicates as hydrothorax and NIHF (11). As explained by Starling's Principle, raised central venous pressure also leads to hydrops due to minimal fluid reabsorption (11).

Development of Foetal Hypoxia

Foetal asphyxia or heart failure promotes the retention of fluid resulting in polyhydramnios and NIHF. Furthermore, angiotensin receptors in the umbilical artery epithelium induce

vasoconstriction, such that the foetus retains more water and salt from the placenta, causing renal impairment. Oliguria and anuria augment hydrops (11).

At early gestation, the ductus venosus is still not responsive to catecholamines and so, smooth muscle layers of the intra-hepatic veins are stimulated to vasoconstrict.

This may result in liver failure due to hypoxic damage, such that less albumin is synthesised; lowering oncotic pressure inside the capillary and enhancing NIHF formation (11). Atrial natriuretic peptide is also released from atrial myocytes when central venous pressure is high and ventricular distension occurs (24). This lowers blood pressure by inducing vasodilation and increasing capillary permeability (25).

Conclusion

It is evident that there is substantial knowledge about the pathophysiology of HF. Furthermore, the importance of understanding this is essential for the advancements in the treatment of the condition. Being that the etiologies of HF are diverse, this makes finding a treatment highly dependent on the diagnosis of the cause in a timely manner (4).

The pathophysiologies of certain causes of NIHF are still unknown, thus making treating such a condition significantly harder. Although advancements made have resulted in a significant decrease in mortality, namely in regards to IHF, HF is still notable, and thus, research on this front is still highly sought after (4).

References

1. Trainor B, Tubman R. The emerging pattern of hydrops fetalis--incidence, aetiology and management. Ulster Med J. 2006 Sep;75(3):185–6.

2. Bukowski R, Saade GR. Hydrops fetalis. Clin Perinatol. 2000 Dec;27(4):1007–31.

3. Ratanasiri T, Komwilaisak R, Sittivech A, Kleebkeaw P, Seejorn K. Incidence, causes and pregnancy outcomes of hydrops fetalis at Srinagarind Hospital, 1996-2005: a 10-year review. J Med Assoc Thai. 2009 May;92(5):594–9.

4. Nassr AA, Ness A, Hosseinzadeh P, Salmanian B, Espinoza J, Berger V, et al. Outcome and treatment of antenatally diagnosed nonimmune hydrops fetalis. Fetal Diagn Ther. 2018;43(2):123–8.

5. Takci S, Gharibzadeh M, Yurdakok M, Ozyuncu O, Korkmaz A, Akcoren Z, et al. Etiology and outcome of hydrops fetalis: report of 62 cases. Pediatr Neonatol. 2014 Apr;55(2):108–13.

6. Singla S, Kumar S, Roy KK, Sharma JB, Kachhawa G. Severe hydrops in the infant of a Rhesus D-positive mother due to anti-c antibodies diagnosed antenatally: a case report. J Med Case Reports. 2010 Feb 18;4:57.

7. Agarwal K, Rana A, Ravi AK. Treatment and prevention of rh isoimmunization. J Fetal Med. 2014 Jun;1(2):81–8.

8. Liumbruno GM, D'Alessandro A, Rea F, Piccinini V, Catalano L, Calizzani G, et al. The role of antenatal immunoprophylaxis in the prevention of maternal-foetal anti-Rh(D) alloimmunisation. Blood Transfus. 2010 Jan;8(1):8–16.

9. Snowise S, Johnson A. Immune Hydrops Fetalis. Obstetric imaging: fetal diagnosis and care. Elsevier; 2018. p. 526-532.e1.

10. Apkon M. Pathophysiology of hydrops fetalis. Semin Perinatol. 1995 Dec;19(6):437–46.

11. Bellini C, Hennekam RCM. Non-immune hydrops fetalis: a short review of etiology and pathophysiology. Am J Med Genet A. 2012 Mar;158A(3):597–605.

12. Butler MJ, Down CJ, Foster RR, Satchell SC. The pathological relevance of increased endothelial glycocalyx permeability. Am J Pathol. 2020 Feb 6;190(4):742–51.

13. Bernier-Latmani J, Sabine A, Petrova TV. Development and differentiation of the lymphatic vascular system. In: Schmidt MH, Liebner S, editors. Endothelial signaling in development and disease. New York, NY: Springer New York; 2015. p. 115–33.

14. Tammela T, Alitalo K. Lymphangiogenesis: Molecular mechanisms and future promise. Cell. 2010 Feb 19;140(4):460–76.

15. Moore JE, Bertram CD. Lymphatic System Flows. Annu Rev Fluid Mech. 2018 Jan;50:459–82.

16. Underwood MA, Gilbert WM, Sherman MP. Amniotic fluid: not just fetal urine anymore. J Perinatol. 2005 May;25(5):341–8.

17. Hua Y, Jiang W, Zhang W, Shen Q, Chen M, Zhu X. Expression and significance of aquaporins during pregnancy. Front Biosci (Landmark Ed). 2013 Jun 1;18:1373–83.

18. Krywko DM, Jamal Z, Shunkwiler SM. Kleihauer Betke Test. StatPearls. Treasure Island (FL): StatPearls Publishing; 2020.

19. De Groot CJ, Oepkes D, Egberts J, Kanhai HH. Evidence of endothelium involvement in the pathophysiology of hydrops fetalis? Early Hum Dev. 2000 Mar;57(3):205–9.

20. Basu S, Kaur R, Kaur G. Hemolytic disease of the fetus and newborn: Current trends and perspectives. Asian J Transfus Sci. 2011 Jan;5(1):3–7.

21. Pegoraro V, Urbinati D, Visser GHA, Di Renzo GC, Zipursky A, Stotler BA, et al. Hemolytic disease of the fetus and newborn due to Rh(D) incompatibility: A preventable disease that still produces significant morbidity and mortality in children. PLoS ONE. 2020 Jul 20;15(7):e0235807.

22. Rudolph AM. Congenital cardiovascular malformations and the fetal circulation. Arch Dis Child Fetal Neonatal Ed. 2010 Mar;95(2):F132-6.

23. Gournay V. The ductus arteriosus: physiology, regulation, and functional and congenital anomalies. Arch Cardiovasc Dis. 2011 Nov;104(11):578–85.

24. Hofstaetter C, Gudmundsson S. Venous Doppler in the evaluation of fetal hydrops. Obstet Gynecol Int. 2010 May 5;2010:430157.

25. Thakur V, Fouron J-C, Mertens L, Jaeggi ET. Diagnosis and management of fetal heart failure. Can J Cardiol. 2013 Jul;29(7):759–67.

Author:
Maria Nastasia Hudson

Reviewers:
Prof. Mauro Pessia
Dr. Ian Said Huntingford

Irritable Bowel Syndrome Overview

Introduction

Irritable bowel syndrome (IBS) is one of the most common disorders of the gastrointestinal tract, affecting around ten to fifteen percent of individuals worldwide, and is especially prevalent in the Western World (Raskov, Hans et al., 2016). The disorder may manifest in different forms ranging from mild to severe, but the commonest symptoms include frequent occurrences of bloating, abdominal pain and altered bowel habits presenting as either constipation (IBS-C) , diarrhea (IBS-D) or the interchanging of the two (IBS-M) as described by the Rome IV Classification (Figure 1) . IBS is not a life-threatening condition, however; it is highly uncomfortable and painful. In fact, other symptoms may also be common such as lack of sleep and depression due to the low quality of life associated with the condition (Canavan, C et al., 2014). Despite the fact that IBS is a gastrointestinal disorder, it is becoming increasingly evident that both the microbiome and the brain play major roles in the development and manifestation of this condition.

The gut-brain axis (GBA) is a term used to describe the bidirectional relationship between the central nervous system and the gastrointestinal tract (Collins, S.M et al., 2009). This axis describes a crucial relationship that must be considered in patients suffering from many inflammatory bowel disorders and irritable bowel syndrome.

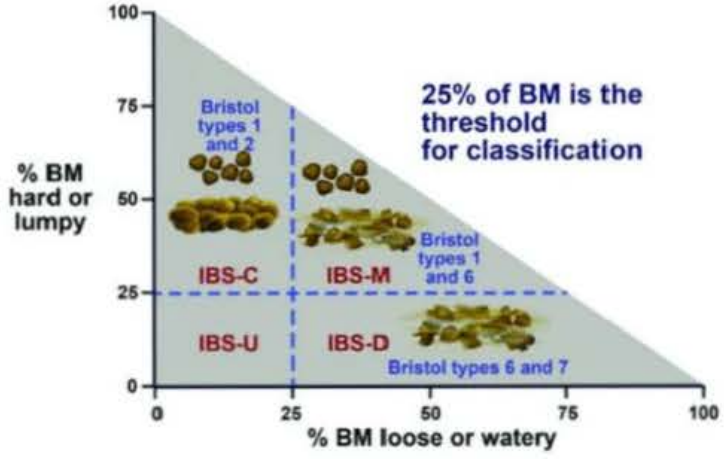

Figure 1: (Source- Menees, Stacey et al. 2018)

The above graph, % Bowel Movement (BM) hard or lumpy against % BM loose or watery, illustrates the different IBS subgroups according to both the Rome IV and the Bristol Stool Form Scale. Individuals having IBS with loose or watery stools >25% of the time have IBS-D (IBS with diarrhea) or Bristol Type 6 and 7 whilst those having IBS with hard or lumpy stools >25% of the time are classified as having IBS-C (IBS with constipation) or Bristol Type 1 and 2. Individuals having a mixture of stool consistencies are classified as having IBS-M (IBS with a mixed pattern) or Bristol Type 1 and 6. IBS-U is a term used to group those individuals having a type of IBS which is, as of yet, unclassified.

The role of the microbiome and irritable bowel syndrome

There are numerous microorganisms inhabiting the human gut, most notably in the last part of the small intestine and the colon. Bacteria are the most predominant microorganisms. However, fungi and viruses may be found to a lesser extent (Menees, Stacey et al., 2018). Ninety-three percent of the bacterial species are from the phyla Bacteroidetes, Actinobacteria, Proteobacteria and Firmicutes (Turnbaugh, P.J. et al., 2007). It is important to note that the microbiome is influenced by many factors.

In fact, several studies have suggested that lifestyle factors such as diet, drugs and exercise have a critical role in influencing the microbiome and its composition, more so than genetic influences. Moreover, the composition of the microbiome is an important factor in predicting many conditions such as diabetes, obesity, and even IBS (Musso, Giovanni et al., 2010).

Bacteria in the microbiome are crucial for health. These bacteria provide the human diet with essential amino acids, vitamins, and fatty acids as well as influence normal gut development and function. This is shown by studies involving animals that lack gut bacteria, which also have reduced gut function and motility when compared to those animals having a normal collection of gut microbiota (Menees, Stacey et al., 2018). It is interesting to note that under normal circumstances, there is immune homeostasis in the gut environment that allows bacteria to carry out their symbiotic function. However, if the intestinal barrier is breached by the entry of various inflammatory mediators or pathogenic organisms, homeostasis is lost and inflammation results (Pedron T., Sansonetti P., 2008). The inflammatory reaction may result in a dysregulated microbiome which may be the linked to the pathophysiology of irritable bowel syndrome namely due to changes occurring in the connections of the gut-brain axis (Chong, P.P et al., 2019).

The relationship between dysbiosis, lack of diversity of gut microbes, and irritable bowel syndrome development was consolidated by many studies (Carroll I.M. et al., 2012). These studies have demonstrated that IBS development is positively related to factors associated with dysbiosis such as low methane expiration. This relation is further supported by the beneficial effects of probiotics on relieving gut inflammation and sensitivity and thus inflammatory bowel syndrome (Ohmna L. , Simren M., 2013).

IBS susceptibility and the diet's role in IBS development

It should be noted that patients who are diagnosed with IBS are, in general, divided into two distinct subgroups: sporadic and post-infectious. Those patients with sporadic IBS are the ones who have had long-term IBS symptoms with no event correlation, whilst patients with post-infectious IBS are those who developed IBS symptoms after gastroenteritis. The latter make up around six to seventeen percent of patients suffering from IBS (Longstreth, G.F. et al., 2001). Thus, IBS susceptibility is highly linked to bowel inflammation as explained earlier. This being said, IBS etiology is not altogether understood.

However, several studies have indicated that the development of this condition may be dependent on the interplay between the microbiome, genetics, as well as the diet (El Salhy, Magdy et al.,2019). It is for this reason that IBS development is thought to be multifactorial.

The diet plays a crucial role in IBS patients. Patients suffering from IBS report that certain food items, such as milk products and beans, worsen IBS symptoms and therefore the control of dietary factors may be a means of treatment for IBS patients (El Salhy, M. et al. 2014). It was found that a diet low in fermentable oligo-, di-, mono-saccharides and polyols (FODMPs) improves IBS-related symptoms and may, by extension, be beneficial to patients. However, a low FODMP diet seems to have various negative repercussions both in the short and long-term. Firstly, only around fifty percent of IBS patients seem to respond to a low FODMP diet and thus the diet is less effective than was previously thought. Secondly, low adherence is not uncommon due to the fact that this form of diet is costly, and thirdly, in the long- term a low FODMP diet seems to have a negative impact on the microbiome itself, which may incongruously even worsen IBS symptoms (Eswaran, S.L et al., 2016) The National Institute for Health and Care Excellence (NICE) proposed an effective and less harmful diet for IBS patients, which is nowadays the first-line diet

Vegetables	Fruits	Others
Onions, garlic, beans, peas, artichoke, cabbage	Watermelon	Wheat flour and wheat-based products Milk and dairy products Sweeteners containing fructose (for example, corn syrup) Sweeteners: sorbitol, menthol, xylitol, isomalt, maltitol, and other sweeteners with names ending in "ol" Carbonated drinks (soft drinks), coffee, beer

Table 1 ; (Source: El Salhy, Magdy et al.,2019) The above table indicates the items of food to be avoided by IBS patients according to the NICE Irritable Bowel Syndrome guidelines. It includes vegetables, fruits, and numerous other products that one must avoid in order to better control IBS-related symptoms.

indicated for these individuals. The diet proposed to these patients entails eating regular meals as well as reducing the intake of beans, carbonated drinks, fatty foods, and others (Table 1).

Conclusion

As clearly explained above, IBS is a condition which affects numerous individuals across the world. It negatively impacts the patient's quality of life and the impact is equal to that caused by various other chronic conditions such as kidney failure and diabetes (Gralnek, I.M. et al., 2000). Despite how common and disabling the syndrome is, there are no true effective treatments. In fact, the treatments and medications prescribed are ones that can only manage the condition by alleviating the symptoms. Thus, further research and studies are necessary in order to work towards a better understanding of the etiology behind IBS in order to effectively treat and manage patients suffering from this syndrome.

References

(1) Gralnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health-related quality of life. Gastroenterology 2000;119(3):654-660.

(2) El-Salhy M, Gilja OH, Gundersen D, Hatlebakk JG, Hausken T. Interaction between ingested nutrients and gut endocrine cells in patients with irritable bowel syndrome. Int J Mol Med 2014;34(2):363-371.

(3) Eswaran SL, Chey WD, Han-Markey T, Ball S, Jackson K. A randomized controlled trial comparing the low FODMAP diet vs. modified NICE guidelines in US adults with IBS-D. Am J Gastroenterol 2016;111(12):1824-1832.

(4) Longstreth GF, Hawkey CJ, Mayer EA, Jones RH, Naesdal J, Wilson IK, et al. Characteristics of patients with irritable bowel syndrome recruited from three sources: implications for clinical trials. Aliment Pharmacol Ther 2001;15(7):959-964.

(5) El-Salhy M, Hatlebakk JG, Hausken T. Diet in irritable bowel syndrome (IBS): Interaction with gut microbiota and gut hormones. Nutrients 2019;11(8):1824.

(6) Carroll IM, Ringel-Kulka T, Siddle JP, Ringel Y. Alterations in composition and diversity of the intestinal microbiota in patients with diarrhea-predominant irritable bowel syndrome. Neurogastroenterology & Motility 2012;24(6):521-e248.

(7) Öhman L, Simrén M. Intestinal microbiota and its role in irritable bowel syndrome (IBS). Curr Gastroenterol Rep 2013;15(5):323.

(8) Chong PP, Chin VK, Looi CY, Wong WF, Madhavan P, Yong VC. The microbiome and irritable bowel syndrome–a review on the pathophysiology, current research and future therapy. Frontiers in microbiology 2019;10:1136.

(9) Pédron T, Sansonetti P. Commensals, bacterial pathogens and intestinal inflammation: an intriguing menage a trois. Cell host & microbe 2008;3(6):344-347.

(10) Musso G, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? Diabetes Care 2010;33(10):2277-2284.

(11) Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. Nature 2007;449(7164):804-810.

(12) Menees S, Chey W. The gut microbiome and irritable bowel syndrome. F1000Research 2018;7.

(13) Raskov H, Burcharth J, Pommergaard H, Rosenberg J. Irritable bowel syndrome, the microbiota and the gut-brain axis. Gut microbes 2016;7(5):365-383.

(14) Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clinical epidemiology 2014;6:71.

(15) Collins SM, Bercik P. The relationship between intestinal microbiota and the central nervous system in normal gastrointestinal function and disease. Gastroenterology 2009;136(6):2003-2014.

Author:
Daniela Chatlani

Reviewers:
Prof. Julian Mamo
Prof. Victor Grech

Repercussions of Home Confinement during the COVID-19 Pandemic

Abstract

The COVID-19 pandemic has disrupted almost all aspects of one's daily routine which has lead to unprecedented stress and other mental consequences. This, coupled with home confinement has lead to a change in the nutrional and exercise habits of the population, both positive and negative. The purchase of calorie-dense foods has been increased and so has boredom eating however given that more time is being spent at home, many people are opting to cook more. Home confinement has also lead to an increase in sedentary behaviour but some have found more time to pursue exercise as a form of leisure. The following changes could lead to an increase in obesity, which in itself is already one of the problems that Malta has been facing these last few years.

Tags: nutrition, exercise, obesity, pandemic

Introduction

The year 2020 has been dominated by the COVID-19 pandemic which originated in Wuhan, China in December 2019. The WHO declared the SARS-CoV-2 outbreak as a pandemic on 11th March 2020. Since this virus is primarily spread through small droplets, most governments have enforced lockdowns and other restrictions in order to minimise further spreading of the virus, with Malta implementing a partial lockdown on 28th March (Grech V. 2020).

Isolation and confinement have been proven to be beneficial to contain and limit the spread of disease (Duerr et al. 2007). This however has had many mental repercussions on many individuals, with increased risk of depression, boredom, and anxiety (Wang et al. 2020). With such emotions many people will no longer prioritise their health.

This has caused an enormous change in the routine of many people's lives.

While for some this can be considered as a small vacation from their normal lives, for many this has been a time of uncertainty. In a study about how emotions affect human appetite, changes in food intake have been observed in times of stress and other heightened emotional states (Macht et al. 2008). The nutritional status of individuals can be taken as an indicator of the resilience against destabilisation (Naja et al. 2020). One can therefore presume that in some individuals there have been changes in their diet.

With the closure of gyms and other recreational centres, one can also expect a change in the energy expenditure of many individuals (Naja et al. 2020). On the other hand many people found themselves with more free time to pursue hobbies which they may not have had time to do before and some of these hobbies could have included a degree of exercise.

Nutrition

One of the main pillars of maintaining a healthy lifestyle is adequate nutrition. The deviation from the normal routine will certainly have an effect on this. Even short deviations from routine such as on vacations usually result in weight gain. (Cooper et al. 2016). Literature shows that even in this short amount of time there can be disruptions in eating behaviours which usually lean towards an energy surplus, leading to increased fat formation (Bhutani et al. 2020). The most at risk to this phenomenon are those individuals which are overweight however even the most physically active are not necessarily protected from this effect (Stevenson et al. 2013). The public health measures imposed due to the pandemic have certainly caused a deviation from the normal well-established routines of many people's lives and so one can cautiously expect to see a similarity between effects caused by vacation and effects caused by the pandemic (Bhutani et al. 2020)

Studies have indicated that households have increased their purchasing of calorie-dense ultraprocessed foods (Bhutani et al. 2020). In the beginning there was also a fear of food running out which led to the purchase of many long-lasting preserved foods (Food Insight). This has made access to high-calorie food much easier. An initial study of Google trends has shown that while there was an increase in the searches for 'recipe' in April, there was also a decline in the searches for 'healthy eating'. Around March there was also a surge in searches for the term 'boredom' which can reflect the feelings of the general population (Goldman D. 2020). Boredom, coupled with anxiety, can lead to more frequent eating (Sominsky et al. 2014). An Australian study which surveyed 5289 individuals indicated that 34.6% of them

has engaged in binge eating during the lockdown (Phillipou et al. 2020). Limited culinary ability can also contribute negatively to nutrition (Ribeiro et al. 2020).

However, the social distancing measures imposed also present an opportunity for many to change previous bad nutrition habits. The purchase of more food coupled with an increase in free time for most people has given ample opportunity for more home cooked meals. In the case of university students, many are pressured by social media to be healthy (Sogari et al. 2018) so this may provide a further incentive to have good eating habits.

Exercise

For many university students and other youths physical activity is achieved during their time spent at university, either during movement around or to and from campus or through sport participation (Hoffmann B et al, 2019). The closure of universities, gyms and other recreational centres therefore point to a decrease in activity. Sedentary behaviours also increase in confined environments which leads to less energy expenditure (Hobbs et al. 2014). A study conducted by Phillipou et al. (2020) indicated that almost half of its respondents were exercising less than they would before the pandemic.

Although places that are specifically designated for exercise are closed, this does not mean that people are unable to exercise. The increase in popularity of home fitness products has increased throughout the years due to their convenience and safety. Many home fitness apps allow not only the user to track their workouts but also provide a sense of community in the same way a gym does (Nyenhuis et al. 2020). Moreover even basic exercise such as walking could still be done as long as social distancing is maintained. Since outings are restricted many have opted for the latter with a study reporting a 34.3% increase in exercise (Phillipou et al. 2020).

Implications for the future

Poor diet quality has been associated with a high body mass index (BMI), a decrease in the gut microbiome diversity and also poor mental health (Hislop et al. 2006). The ramifications of physical inactivity include negative effects on glucose homeostasis and metabolic health (Narici et al. 2020). Physical inactivity is considered one of the most important risk factors for major disease morbidity (Hallal et al. 2012) and is also associated with a decreased immune response and more severe cardiopulmonary complications (Bloch et al. 2020). Malta already has an

obesity crisis with a third of the population falling in this category (Cuschieri S et al. 2016). Obesity is associated with a multitude of non-communicable illnesses such as diabetes mellitus, hypertension, and gall bladder disease (Bray et al. 2000). In 2016 this crisis was estimated to cost around €3.6 million spread across pharmaceuticals, hospital care and primary care. Assuming that the obesity rate had remained the same as in 2016, the projected cost of taking care of the obesity crisis was expected to reach €5.1 million by 2022. (PWC: Weighing the cost of Obesity). With the pandemic, it is likely that the obesity rate will increase and will further increase the cost, as well as the burden on our health system.

References

Food Insight (2020). Consumer Survey: COVID-19's Impact on Food Purchasing, Eating Behaviours and Perceptions of Food

Initial Observations of Psychological and Behavioural Effects of COVID-19 in the United States, Using Google Trends Data (Published April 4, 2020)(2020). . Respiratory Therapeutics Week.

1C, L M University, Leeds, UK 2S S, E Health Sciences, Loughborough University, Loughborough, UK 3T NIHR L Loughborough Diet, Lifestyle, Physical Activity Biomedical Research Unit [Now at Institute of Sport, Exercise, Active Living, Victoria University, Melbourne & Australia] Matthew Hobbs,1 Natalie Pearson,2 Perry J Foster,2 Stuart J H Biddle2,3, DOI: 10.1136/bjsports-2014-093754.

Bhutani S, Wells N, Finlayson G & Schoeller DA (2020). Change in eating pattern as a contributor to energy intake and weight gain during the winter holiday period in obese adults. Int J Obes (Lond), DOI: 10.1038/s41366-020-0562-2 [doi].

Duerr HP, Brockmann SO, Piechotowski I, Schwehm M & Eichner M (2007). Influenza pandemic intervention planning using InfluSim: pharmaceutical and non- pharmaceutical interventions. BMC Infect Dis7, DOI: 1471-2334-7-76 [pii].

Gans, Kim M. et al. Development and Evaluation of the Nutrition Component of the Rapid Eating and Activity Assessment for Patients (REAP): A New Tool for Primary Care Providers. Journal of Nutrition Education and Behavior38.

Grech V (2020). Malta's healthcare escalation for COVID-19. null43, DOI: 10.1080/17453054.2020.1768830.

Hoffmann B, Kobel S, Wartha O, Kettner S, Dreyhaupt J & Steinacker JM (2019). High sedentary time in children is not only due to screen media use: a cross-sectional study. BMC pediatrics19, DOI: 10.1186/s12887-019-1521-8.

Macht M (2008). How emotions affect eating: a five-way model. Appetite50, DOI: S0195-6663(07)00323-6 [pii].

Naja F & Hamadeh R (2020). Nutrition amid the COVID-19 pandemic: a multi-level framework for action. European journal of clinical nutrition, DOI: 10.1038/s41430-020-0634-3.

Narici M, De Vito G, Franchi M, Paoli A, Moro T, Marcolin G, Grassi B, Baldassarre G, Zuccarelli L, Biolo G, di Girolamo FG, Fiotti N, Dela F, Greenhaff P & Maganaris C (2020). Impact of sedentarism due to the COVID-19 home confinement on neuromuscular, cardiovascular and metabolic health: Physiological and pathophysiological implications and recommendations for physical and nutritional countermeasures. Eur J Sport Sci, DOI: 10.1080/17461391.2020.1761076 [doi].

Nyenhuis SM, Greiwe J, Zeiger JS, Nanda A & Cooke A (2020). Exercise and Fitness in the Age of Social Distancing During the COVID-19 Pandemic. J Allergy Clin Immunol Pract, DOI: S2213-2198(20)30396-2 [pii].

Phillipou A, Meyer D, Neill E, Tan EJ, Toh WL, Van Rheenen TE & Rossell SL (2020). Eating and exercise behaviours in eating disorders and the general population during the COVID -19 pandemic in Australia: Initial results from the COLLATE project. International Journal of Eating Disorders, DOI: 10.1002/eat.23317.

Ribeiro, K D D S, Garcia LRS, Dametto, J F D S, Assuncao DGF & Maciel BLL (2020). COVID-19 and Nutrition: The Need for Initiatives to Promote Healthy Eating and Prevent Obesity in Childhood. Child Obes16, DOI: 10.1089/chi.2020.0121 [doi].

Sogari G, Velez-Argumedo C, Gomez MI & Mora C (2018). College Students and Eating Habits: A Study Using An Ecological Model for Healthy Behaviour. Nutrients10, DOI: E1823 [pii]

Sominsky L & Spencer SJ (2014). Eating behavior and stress: a pathway to obesity. Frontiers in psychology5, DOI: 10.3389/fpsyg.2014.00434.

for More Than 5 Years. Journal of Clinical Oncology24, DOI: 10.1200/JCO.2005.04.3042

Stevenson JL, Krishnan S, Stoner MA, Goktas Z & Cooper JA (2013). Effects of exercise during the holiday season on changes in body weight, body composition and blood pressure. European journal of clinical nutrition67, DOI: 10.1038/ejcn.2013.98.

T. Gregory Hislop, Chris D. Bajdik, Lynda G. Balneaves, Andrea Holmes, Selina Chan, Evelyn Wu, Zenaida U. Abanto & Andrea L. Butler (2006). Physical and Emotional Health Effects and Social Consequences After Participation in a Low-Fat, High-Carbohydrate Dietary Trial for More Than 5 Years. Journal of Clinical Oncology24, DOI: 10.1200/JCO.2005.04.3042

Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS & Ho RC (2020). Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. Int J Environ Res Public Health17, DOI: E1729 [pii].

Wanner M, Hartmann C, Pestoni G, Martin BW, Siegrist M & Martin-Diener E (2017). Validation of the Global Physical Activity Questionnaire for self-administration in a European context. BMJ Open Sport & Exercise Medicine3, DOI: 10.1136/bmjsem-2016-000206

Author:
Adrienne Gatt

Reviewers:
Prof. Therese Hunter
Dr. James DeGaetano

The Effect of Fibre in Fruit and Vegetables on Colorectal Cancer

Fibre is defined as indigestible remnants of plant carbohydrates. They are classified as indigestible as they cannot be broken down by the body's enzymes (Perez-Cueto and Verbeke 2012). It is a major component in fruit and vegetables, as well as in other foods such as cereals and grains. Increase in dietary fibre intake is shown to lower the risk of colorectal cancer (CRC) development, especially with respect to distal colon cancer (Kunzmann et al., 2015). Generally, an intake of 10g of fibre daily has shown to reduce CRC risk by 10% (Song et al., 2018). This, however, mainly refers to the progression of adenomas to CRC. (Kunzmann et al., 2015). Moreover, evidence has shown that patients who ingested greater amounts of fibre prior to being diagnosed with CRC tended to have a lower mortality rate, with CRC mortality decreasing by 18% with every 5g of fibre consumed. Studies conducted by Kunzmann et al., (2015) did not establish any strong relationships between risk of recurring adenomas and fibre intake, irrespective of the source of fibre, site of adenoma or adenoma progressivity. Research also showed that increasing fibre consumption post-diagnosis of CRC can increase survival chances (Song et al., 2018).

Fibre is classified into 3 different categories: soluble; insoluble; and pectins. They exhibit different degrees of association with CRC risk, with a strong inverse linear effect between insoluble fibre intake and CRC risk (Navarro et al., 2016). Patients consuming greater amounts of fibre are more likely to present with stage I CRC rather than stages II or III, which are more severe. (Song et al., 2018). An effect was also recorded for fibre from cereal and vegetables, with cereal fibre imposing a more potent effect on CRC reduction compared to vegetable fibre, due to its greater fibre content (Ben et al., 2014 as cited by Navarro et al., 2016). On the other hand, no relationship was established between CRC risk and fibre from fruit (Song et al., 2018) except for Kunzmann et al., (2015) who reported a strong protective relationship in fruit

fibre. Such discrepancies may potentially be due to cereal fibre being insoluble, in contrast to fibre in both fruit and vegetables, which tends to be more soluble (Terry et al., 2001). Both the extent of tumour differentiation as well as the site of tumour origin did not vary in relation to dietary fibre consumption from any food source.

The fibre component of fruit and vegetables provides protection against carcinogens. This is done by decreasing the concentration of toxins within faeces by means of bulking, ultimately diminishing the transit time of carcinogenic contents within the colon (Burkitt 1971). This in turn limits the generation of secondary bile acids, preventing the production of reactive oxygen species (ROS). (Young et al., 2005). It also has a regulatory effect over metabolism as well as insulin sensitivity, and so is considered to be associated with the prognosis of CRC (Brown and Meyerhardt 2016). Insulin markers, inflammation and hyperinsulinemia have shown to aggravate CRC prognosis, potentially resulting in recurrence and even death. (Cespedes Feliciano et al., 2016; Volkova et al., 2011). Therefore, increasing fibre intake through vegetables and fruit can reduce carcinogenic traits and improve CRC prognosis (Song et al., 2018).

Fibre reduces the risk of CRC mainly through fermentation, by producing anti-tumorigenic short-chain fatty acids such as butyrate, acetate and propionate, via gut microbiota (Bultman 2014; Encarnacao et al., 2015). Butyrate is a crucial source of energy for normal colonic enterocytes, stimulating the production of ROS and creating an oxidative environment (Kolar et al., 2011). However, it is used to a lesser extent in tumorigenic cells. Butyrate ends up accumulating in the nucleus of these cancerous cells, hindering the enzyme histone deacetylase and ultimately altering gene expression in relation to angiogenesis, tumour cell growth and metastasis (Encarnacao et al., 2015). Inhibition of this enzyme also gives butyrate the ability to trigger apoptosis within cancerous cells, stimulating the extrinsic death pathway (Donohoe et al., 2012). Therefore, butyrate and other compounds produced from fibre by fermentation can act as chemotherapeutic agents with respect to CRC (Bras-Gonçalves et al., 2001). Unfortunately, it is still unclear as to what point in carcinogenesis does fibre exert its anti-tumorigenic properties.

Fibre's protective traits are more significant with increased consumption of processed meat (Kunzmann et al., 2015). This results in a reduced exposure of the colon to carcinogens found in processed meat, such as N-nitrosis compounds (NOCs) (Santarelli et al., 2008). Increased processed meat intake augments the risk and development of CRC. Therefore, one can promote consumption of fibre to reduce the risk induced by processed meat. Other lifestyle factors unrelated to diet, like

smoking, can also alter the effect of dietary fibre on CRC risk (Botteri et al., 2008 as cited by Fu et al., 2013). The inverse relationship of fibre and CRC risk is generally stronger in smokers compared to non-smokers. However, smoking intensity is not a determining factor in this association (Fu et al., 2013). Fibre is able to dilute the concentration of carcinogens derived from cigarette smoke in faeces, thus diminishing the degree of contact of such carcinogens with the lumen of the colon (Lipkin et al., 1999 as cited by Fu et al., 2013). Ultimately, cigarette smoking increases the chances of developing CRC, but the extent to which it can be induced is diminished when coupled with an increase in dietary fibre.

The Colour of Fruit and Vegetables and its Influence on Colorectal Cancer

An increase in both fruit and vegetable consumption tends to decrease the risk of CRC. A stronger association exists with respect to raw vegetables in comparison to cooked vegetables, due to a lack of nutrient breakdown (Link and Potter 2004 as cited by Lee et al., 2017). In women, an inverse relationship has been recorded between CRC risk and red, green and white fruit and vegetables. The same applies for males, with the exception of yellow and orange fruit and vegetables, such as carrots, pumpkin and citrus fruits, which promote the development of CRC (Lee et al., 2017). Green fruit and vegetables possess the advantageous property of high concentrations of pro-apoptotic substances such as indole, folate, sulforphane, and lutein. They inhibit tumour cell growth and reduce cell damage (Frydoonfar et al., 2004; Nishikawa et al., 2010).

White fruit and vegetables contain different phytochemicals, all of which exert anti-tumorigenic properties. Examples include saponins present in bulb vegetables such as garlic; glucans found in mushrooms; and polysaccharides in apples. These compounds are all anti-oxidants and can decrease the likelihood of DNA damage (Li et al., 2015). Many studies on apples show a strong inverse association or no association at all with CRC risk (Jedrychowski and Maugeri 2009). Studies have also proven that garlic has the potential to promote apoptosis, whilst inhibiting progression of the cell cycle and formation of DNA adducts. However, results have shown to be inconsistent and overall conclusions have been made that garlic does not have a significantly established relationship with reduced CRC risk. (Hu et al., 2014). Citrus fruits form part of the yellow and orange fruit and vegetables group, and were found to lower the chances of CRC development in women (Levi et al., 1999 as cited by Lee et al., 2017).

They are highly rich in carotene, which regulates proliferation and metastasis of tumour cells. Similar to white fruit and vegetables, they also have anti-oxidant properties which can hinder CRC development (Liu 2004; Reczek and Chandel 2015). However, consumption of yellow fruit and vegetables can have a pro-cancerous effect on males, with respect to CRC development (Lee et al., 2017). Ginger, however, is an exception to this group. Fresh extraction of ginger root contains gingerol, which is known to hinder progression of CRC in humans due to its ability to inhibit HCT116, a human colon cancer cell line (Zick et al., 2015; Bode 2003). However, rotting ginger contains safrole, a classified carcinogen shown to promote CRC in studies conducted on rodents (Long et al., 1963 as cited by Lee et al., 2017).

Overall, fruit and vegetable consumption tend to decrease CRC risk, with the exception of the yellow and orange colour group. Fibre intake from vegetables also contributes to reduced CRC risk. Therefore, fibre-based diets, containing food such as cereals, grains, fruit and vegetables, should always be promoted, especially amongst those individuals who are susceptible to the development of CRC. By implementing this type of diet, the risk of CRC development is reduced significantly in the individual and is also associated with a decreased incidence of CRC in the general population. There is still need for more research on these relationships in order to better understand the mechanisms by which CRC is induced or inhibited, and to explore potential preventative methods or treatments.

References

Bellavia, A., Larsson, S.C., Bottai, M., Wolk, A. & Orsini, N. 2013, "Fruit and vegetable consumption and all-cause mortality: a dose-response analysis", The American Journal of Clinical Nutrition, vol. 98, no. 2, pp. 454-459.

Ben, Q., Sun, Y., Chai, R., Qian, A., Xu, B. & Yuan, Y. 2014, "Dietary fiber intake reduces risk for colorectal adenoma: a meta-analysis", Gastroenterology, vol. 146, no. 3, pp. 689-699.e6.

Bode ADZ. Ginger is an effective inhibitor of HCT116 human colorectal carcinoma in vivo. In: Proceedings of the CANCER EPIDEMIOLOGY BIOMARKERS & PREVENTION; 2003. AMER ASSOC cancer research. USA: Philadelphia, 2003: 1324S-1324S

Botteri, E., Iodice, S., Bagnardi, V., Raimondi, S., Lowenfels, A.B. & Maisonneuve, P. 2008, "Smoking and colorectal cancer: a meta-analysis", Jama, vol. 300, no. 23, pp. 2765-2778.

Bras-Goncalves, R.A., Pocard, M., Formento, J.L., Poirson-Bichat, F., De Pinieux, G., Pandrea, I., Arvelo, F., Ronco, G., Villa, P., Coquelle, A., Milano, G., Lesuffleur, T., Dutrillaux, B. & Poupon, M.F. 2001, "Synergistic efficacy of 3n-butyrate and 5-fluorouracil in human colorectal cancer xenografts via modulation of DNA synthesis", Gastroenterology, vol. 120, no. 4, pp. 874-888.

Brown, J.C. & Meyerhardt, J.A. 2016, "Obesity and Energy Balance in GI Cancer", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 34, no. 35, pp. 4217-4224.

Bultman, S.J. 2014, "Molecular pathways: gene-environment interactions regulating dietary fiber induction of proliferation and apoptosis via butyrate for cancer prevention", Clinical cancer research : an official journal of the American Association for Cancer Research, vol. 20, no. 4, pp. 799-803.

Burkitt, D.P. 1971, "Possible relationships between bowel cancer and dietary habits", Proceedings of the Royal Society of Medicine, vol. 64, no. 9, pp. 964-965.

Cespedes Feliciano, E.M., Kroenke, C.H., Meyerhardt, J.A., Prado, C.M., Bradshaw, P.T., Dannenberg, A.J., Kwan, M.L., Xiao, J., Quesenberry, C., Weltzien, E.K., Castillo, A.L. & Caan, B.J. 2016, "Metabolic Dysfunction, Obesity, and Survival Among Patients With Early-Stage Colorectal Cancer", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 34, no. 30, pp. 3664-3671.

Donohoe, D.R., Collins, L.B., Wali, A., Bigler, R., Sun, W. & Bultman, S.J. 2012, "The Warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation", Molecular cell, vol. 48, no. 4, pp. 612-626.

Encarnacao, J.C., Abrantes, A.M., Pires, A.S. & Botelho, M.F. 2015, "Revisit dietary fiber on colorectal cancer: butyrate and its role on prevention and treatment", Cancer metastasis reviews, vol. 34, no. 3, pp. 465-478.

Frydoonfar, H.R., McGrath, D.R. & Spigelman, A.D. 2004, "Sulforaphane inhibits growth of a colon cancer cell line", Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland, vol. 6, no. 1, pp. 28-31.

Fu, Z., Shrubsole, M.J., Li, G., Smalley, W.E., Hein, D.W., Cai, Q., Ness, R.M. & Zheng, W. 2013, "Interaction of cigarette smoking and carcinogen-metabolizing polymorphisms in the risk of colorectal polyps", Carcinogenesis, vol. 34, no. 4, pp. 779-786.

Hu, J.Y., Hu, Y.W., Zhou, J.J., Zhang, M.W., Li, D. & Zheng, S. 2014, "Consumption of garlic and risk of colorectal cancer: an updated meta-analysis of prospective studies", World journal of gastroenterology, vol. 20, no. 41, pp. 15413-15422.

Jedrychowski, W. & Maugeri, U. 2009, "An apple a day may hold colorectal cancer at bay: recent evidence from a case-control study", Reviews on environmental health, vol. 24, no. 1, pp. 59-74.

Kolar SS, Barhoumi R, Callaway ES, Fan YY, Wang N, Lupton JR & Chapkin RS (2007). Synergy between docosahexaenoic acid and butyrate elicits p53-independent apoptosis via mitochondrial Ca(2+) accumulation in colonocytes. Am J Physiol Gastrointest Liver Physiol 293, G935-43.

Kunzmann, A.T., Coleman, H.G., Huang, W.Y., Kitahara, C.M., Cantwell, M.M. & Berndt, S.I. 2015, "Dietary fiber intake and risk of colorectal cancer and incident and recurrent adenoma in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial", The American Journal of Clinical Nutrition, vol. 102, no. 4, pp. 881-890.

Lee, J., Shin, A., Oh, J.H. & Kim, J. 2017, "Colors of vegetables and fruits and the risks of colorectal cancer", World journal of gastroenterology, vol. 23, no. 14, pp. 2527-2538.

Levi, F., Pasche, C., La Vecchia, C., Lucchini, F. & Franceschi, S. 1999, "Food groups and colorectal cancer risk", British journal of cancer, vol. 79, no. 7-8, pp. 1283-1287.

Li, Y.H., Niu, Y.B., Sun, Y., Zhang, F., Liu, C.X., Fan, L. & Mei, Q.B. 2015, "Role of phytochemicals in colorectal cancer prevention", World journal of gastroenterology, vol. 21, no. 31, pp. 9262-9272.

Link, L.B. & Potter, J.D. 2004, "Raw versus cooked vegetables and cancer risk", Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, vol. 13, no. 9, pp. 1422-1435.

Lipkin, M., Reddy, B., Newmark, H. & Lamprecht, S.A. 1999, "Dietary factors in human colorectal cancer", Annual Review of Nutrition, vol. 19, pp. 545-586.

Liu, R.H. 2004, "Potential synergy of phytochemicals in cancer prevention: mechanism of action", The Journal of nutrition, vol. 134, no. 12 Suppl, pp. 3479S-3485S.

Long EL, Nelson A, Fitzhugh O, Hansen W. Liver tumours produced in rats by feeding safrole. Arch Pathol 1963; 75: 595-604

Navarro, S.L., Neuhouser, M.L., Cheng, T.D., Tinker, L.F., Shikany, J.M., Snetselaar, L., Martinez, J.A., Kato, I., Beresford, S.A., Chapkin, R.S. & Lampe, J.W. 2016, "The Interaction between Dietary Fiber and Fat and Risk of Colorectal Cancer in the Women's Health Initiative", Nutrients, vol. 8, no. 12, pp. 10.3390/nu8120779.

Nishikawa, T., Tsuno, N.H., Okaji, Y., Shuno, Y., Sasaki, K., Hongo, K., Sunami, E., Kitayama, J., Takahashi, K. & Nagawa, H. 2010, "Inhibition of autophagy potentiates sulforaphane-induced apoptosis in human colon cancer cells", Annals of surgical oncology, vol. 17, no. 2, pp. 592-602.

Perez-Cueto, F.J. & Verbeke, W. 2012, "Consumer implications of the WCRF's permanent update on colorectal cancer", Meat Science, vol. 90, no. 4, pp. 977-978.

Reczek, C.R. & Chandel, N.S. 2015, "CANCER. Revisiting vitamin C and cancer", Science (New York, N.Y.), vol. 350, no. 6266, pp. 1317-1318.

Santarelli, R.L., Pierre, F. & Corpet, D.E. 2008, "Processed meat and colorectal cancer: a review of epidemiologic and experimental evidence", Nutrition and cancer, vol. 60, no. 2, pp. 131-144.

Slavin, J.L. & Lloyd, B. 2012, "Health benefits of fruits and vegetables", Advances in nutrition (Bethesda, Md.), vol. 3, no. 4, pp. 506-516.

Song, M., Wu, K., Meyerhardt, J.A., Ogino, S., Wang, M., Fuchs, C.S., Giovannucci, E.L. & Chan, A.T. 2018, "Fiber Intake and Survival After Colorectal Cancer Diagnosis", JAMA oncology, vol. 4, no. 1, pp. 71-79.

Terry P, Giovannucci E, Michels KB, et al., (2001). Fruit, vegetables, dietary fiber, and risk of colorectal cancer. J Natl Cancer Inst; 93(7):525–533. doi:10.1093/jnci/93.7.525

Volkova, E., Willis, J.A., Wells, J.E., Robinson, B.A., Dachs, G.U. & Currie, M.J. 2011, "Association of angiopoietin-2, C-reactive protein and markers of obesity and insulin resistance with survival outcome in colorectal cancer", British journal of cancer, vol. 104, no. 1, pp. 51-59.

Wang, X., Ouyang, Y., Liu, J., Zhu, M., Zhao, G., Bao, W. & Hu, F.B. 2014, "Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies", BMJ (Clinical research ed.), vol. 349, pp. g4490.

Young, G.P., Hu, Y., Le Leu, R.K. & Nyskohus, L. 2005, "Dietary fibre and colorectal cancer: a model for environment--gene interactions", Molecular nutrition & food research, vol. 49, no. 6, pp. 571-584.

Zick, S.M., Turgeon, D.K., Ren, J., Ruffin, M.T., Wright, B.D., Sen, A., Djuric, Z. & Brenner, D.E. 2015, "Pilot clinical study of the effects of ginger root extract on eicosanoids in colonic mucosa of subjects at increased risk for colorectal cancer", Molecular carcinogenesis, vol. 54, no. 9, pp. 908-915.

Cespedes Feliciano, E.M., Kroenke, C.H., Meyerhardt, J.A., Prado, C.M., Bradshaw, P.T., Dannenberg, A.J., Kwan, M.L., Xiao, J., Quesenberry, C., Weltzien, E.K., Castillo, A.L. & Caan, B.J. 2016, "Metabolic Dysfunction, Obesity, and Survival Among Patients With Early-Stage Colorectal Cancer", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 34, no. 30, pp. 3664-3671.

Donohoe, D.R., Collins, L.B., Wali, A., Bigler, R., Sun, W. & Bultman, S.J. 2012, "The Warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation", Molecular cell, vol. 48, no. 4, pp. 612-626.

Encarnacao, J.C., Abrantes, A.M., Pires, A.S. & Botelho, M.F. 2015, "Revisit dietary fiber on colorectal cancer: butyrate and its role on prevention and treatment", Cancer metastasis reviews, vol. 34, no. 3, pp. 465-478.

Frydoonfar, H.R., McGrath, D.R. & Spigelman, A.D. 2004, "Sulforaphane inhibits growth of a colon cancer cell line", Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland, vol. 6, no. 1, pp. 28-31.

Fu, Z., Shrubsole, M.J., Li, G., Smalley, W.E., Hein, D.W., Cai, Q., Ness, R.M. & Zheng, W. 2013, "Interaction of cigarette smoking and carcinogen-metabolizing polymorphisms in the risk of colorectal polyps", Carcinogenesis, vol. 34, no. 4, pp. 779-786.

Hu, J.Y., Hu, Y.W., Zhou, J.J., Zhang, M.W., Li, D. & Zheng, S. 2014, "Consumption of garlic and risk of colorectal cancer: an updated meta-analysis of prospective studies", World journal of gastroenterology, vol. 20, no. 41, pp. 15413-15422.

Jedrychowski, W. & Maugeri, U. 2009, "An apple a day may hold colorectal cancer at bay: recent evidence from a case-control study", Reviews on environmental health, vol. 24, no. 1, pp. 59-74.

Kolar SS, Barhoumi R, Callaway ES, Fan YY, Wang N, Lupton JR & Chapkin RS (2007). Synergy between docosahexaenoic acid and butyrate elicits p53-independent apoptosis via mitochondrial Ca(2+) accumulation in colonocytes. Am J Physiol Gastrointest Liver Physiol 293, G935-43.

Kunzmann, A.T., Coleman, H.G., Huang, W.Y., Kitahara, C.M., Cantwell, M.M. & Berndt, S.I. 2015, "Dietary fiber intake and risk of colorectal cancer and incident and recurrent adenoma in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial", The American Journal of Clinical Nutrition, vol. 102, no. 4, pp. 881-890.

Lee, J., Shin, A., Oh, J.H. & Kim, J. 2017, "Colors of vegetables and fruits and the risks of colorectal cancer", World journal of gastroenterology, vol. 23, no. 14, pp. 2527-2538.

Levi, F., Pasche, C., La Vecchia, C., Lucchini, F. & Franceschi, S. 1999, "Food groups and colorectal cancer risk", British journal of cancer, vol. 79, no. 7-8, pp. 1283-1287.

Author:
Rebecca Caruana

Reviewers:
Prof. Gary Hunter
Prof. Alexander Gatt

Vitamin D Receptor and Cancer

Vitamin D Receptor Structure

Vitamin D target tissues contain a specific vitamin D nuclear receptor (VDR). VDRs are present in more than 30 cell types particularly those responsible for calcium homeostasis, immune function, endocrine, hematopoiesis and tumors. VDR is a 51kDa steroid, thyroid protein hormone. VDR shows more than 95% homology between species. The VDR contains an N-terminal DNA-binding domain (DBD). This acts as a cysteine-rich recognition domain on a sulfhydryl protein. In the C-terminal there is present a ligand-binding domain (LBD). In response to increased parathyroid hormone (PTH) and calcitriol synthesis of the VDR receptor increases (Bak, 2006).

VDR Gene Polymorphisms

Numerous common polymorphisms are located in the VDR gene. Namely FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232) and TaqI (rs731236). The polymorphisms BsmI, ApaI and TaqI are strongly linked with each other as when one polymorphism is presentit can predict the occurrence of the others. In fact they almost always occur with each other. This is known as linkage disequilibrium.

In the DNA sequence FokI is the "start codon." Its function is to signal the position of the protein chain formation in DNA sequence the protein chain. ATG is the DNA sequence for a start codon encoding the amino acid methionine. The VDR gene is composed of two possible start codons which are positioned very close to one another at the initial gene position. At the right, the SNP rs2228570 (T/C) results in methionine (M, Met) substitution. Therefore it becomes encoded by the three-letter codon ATG, for a threonine (T, Thr) amino acid, encoded by ACG at position 1 of the protein (Met1Thr). Therefore this eliminates the first start codon, to result in the use of the second start codon producing a VDR protein. As a result the 'T' allele creates a longer VDR protein which is composed of 427 amino acids than the 'C' allele which creates a shorter VDR protein composed of 424 amino acids. Even though these VDR proteins are of different lengths, both are functional VDR proteins.

On the other hand the BsmI, ApaI and TaqI polymorphisms and other polymorphisms present on the VDR gene, are so close to each other that they are almost always inherited with each other by chance alone. The 'G' allele of BsmI (b), 'G' allele of ApaI (a) and 'T' allele of TaqI (T) are generally detected together forming baT. The alleles 'A' BsmI, 'T' ApaI and 'C' TaqI association forms Bat (Takeshige, 2015). This is summarized in Table 1.

Reference SNP ID	Rs2228570	Rs1544410	Rs7975232	Rs731236
Traditional Name	*FokI*	*BsmI*	*ApaI*	*TaqI*
Allele	T C(G,A)	G A	G T	T C
Traditional Name Variant	f F	B B	A A	T t
Amino Acid	Met Thr	Non-coding	Non-coding	Lie Lie

Table 1. VDR Polymorphisms

Antioxidant effects of Vitamin D and Cancer

Antioxidant Effects

When liganded, VDR can inhibit expression of factors which generate reactive oxygen species (ROS) and factors which remove ROS intracellularly preventing tissue damage. It can upregulate the expression of NADPH oxidase through genomic action or stimulate the synthesis of reactive nitrogenspecies through the influx of Ca2+ into the cells- this is non-genomic promotion. These actions can not only increase cancer cells' sensitivity to drugs but may also promote vascular calcification and fat deposition in adipocytes i.e. major ROS production species Yet more studies are required regarding vitamin D as an antioxidant (Ke et al., 2016).

Colorectal cancer

1,25-(OH)2-D3 can reduce the growth of rapidly dividing colon tumor cells and reverse colonocytes from a malignant to a normal phenotype. These properties are due to VDR activation which inhibits signaling through β-catenin (a mediator of the Wnt pathway). This stimulates apoptosis. On the other hand VDR can also bind to bile acid and lithocholic acid i.e. a potent enteric carcinogen. VDR expression appears to decline during the progression of colon cancer and this has been associated with the upregulation of cancer transcriptional repressors which bind to VDR-promotors shifting catabolism from calcifediol to calcitriol. These suppress the inflammation process. (Takeshige, 2015).

Gupta et al; (2011) enhance how serum 25-0H-D3 levels of more than 20 ng/mLor intakes of a minimum of 1000-2000IU/day show significant reduction in colorectal risk.

VDR single nucleotide polymorphism gene exists which has been associated with differences in colon cancer risk. Cdx-22 AA of FokI TT carriers showed twice the increased risk for colorectal cancer when compared with other genotypes. On the other hand those with Cdx-2-FokIA-T, FokI TaqIT-G, or Cdx-2-FokITaqIA-T-G haplotypes showed two to three fold increased colon cancer risk when compared with other haplotypes (Rai et al; 2017).

The most recent study which shows the relationship between vitamin D and cancer is the SUNSHINE Randomized Clinical Trial (RCT) performed by Ng, et al in 2019. This study has concluded that high vitamin D doses may help to hinder advanced colorectal cancer growth when combined with chemotherapy. In the RCT it was observed that disease progression in the participants of the high-dose group remained stationary for about 13 months in average, while those participants in the low-dose group remained stationary for around 11 months. Also it was observed that the participants before the SUNSHINE trial had low Vitamin D doses. Yet further research is required to identify the advantages of vitamin D in colorectal cancer.

Breast cancer

Breast cells express VDR. Liganded VDR functions in inhibiting growth, inducing apoptosis and stimulating expression factors which are involved in cell proliferation regulation. These function by blocking mitogenic signals which are estrogen-driven. Studies including those performed by Huss et al; (2019) and Al-Azhri et al; (2017) have found an inverse relationship between VDR expression and invasiveness of breast tumors. As in their research, even though more research is required, they have concluded that high VDR expression in invasive breast tumors is associated with favorable prognostic factors and low risk of breast cancer associated death. Therefore having high VDR expression is a positive prognostic factor. In fact Schwalfenberg, Genius & Hiltz (2009) have estimated that in Canada increasing 25-OH-D3 serum levels to 40–60 ng/mL yearly would prevent around 58,000 new cases of breast cancer each year while reduce breast cancer mortality by half.

Prostate cancer

Studies in human prostate cells have shown that calcitriol bind with VDR to bring about androgen signaling. This signaling brings about differentiation of stem cells to androgen-receptor positive epithelial cells while augmenting tumor-suppressing microRNAs. Hendrickson et al; (2011)

have found that circulating 25-hydroxyvitamin D interact with VDR decreasing proliferation and increasing apoptosis for some types of malignancies. Köstner et al; (2009) identified those carriers of the VDR Bsm1 B allele prostate cancer risk is less than those which do not carry the allele.

Skin cancer and polymorphisms

Vitamin D brings about keratinocyte proliferation by inhibition of β-catenin signaling and protection of UV-induced DNA damage. It does this by VDR which brings about upregulation of p53, inhibition of stress-activated kinases and nitric oxide suppression production. In the meta-analysis, Denzer Vogt and Reichrath (2011) studied the risk of melanoma exherted by VDR polymorphisms. The TaqI polymorphism (rs731236) is a restriction fragment length polymorphism (RFLP). In the meta-analysis it was conveyed that TaqI allele t was significantly less frequent among melanoma patients than among controls. Therefore one can deduce that t might confer protection to carriers against melanoma while T increases their risk. On the other hand, genotypes Tt + tt were less frequent among melanoma patients than among controls and were linked with significantly lower melanoma risk for Tt + tt vs. TT genotypes. BsmI polymorphism may alter gene expression by regulation of the stability of mRNA. The BsmI allele B was found to be less frequent among melanoma patients. Therefore one can deduce that B may confer protection for carriers against melanoma while b may put them at risk. The FokI f allele was identified to increase the risk of melanoma.

Conclusion

Throughout this article the role of VDR as an antioxidant and its role in cancer prevention was discussed. It was also seen how VDR polymorphisms confer protection or increase the risk for specific types of cancer. Even though this article enhanced on outbreaking discoveries in cancer prevention regarding VDR further studies are required.

References

Al-Azhri J, Zhang Y, Bshara W, Zirpoli G, McCann SE, Khoury T, Morrison CD, Edge SB, Ambrosone CB & Yao S (2017). Tumor Expression of Vitamin D Receptor and Breast Cancer Histopathological Characteristics and Prognosis. Clinical Cancer Research 23(1).

Bak RS (2006). Vitamin D and Metabolites. Warde Medical Laboratory 17(1).

Denzer N, Vogt T & Reichrath J (2011). Vitamin D receptor (VDR) polymorphisms and skin cancer. DermatoEndocrinology 3(3): 205–210.

Gupta D, Vashi PG, Trukova K, Lis CG, & Lammersfeld CA (2011). Prevalence of serum vitamin D deficiency and insufficiency in cancer: Review of the epidemiological literature. Experimental and Therapeutic Medicine 2(2): 181–193.

Hendrickson WK, Flavin R, Kasperzyk JL, Fiorentino M, Fang F, Lis R, Fiore C, Penney KL, Ma J, Kantoff PW, Stampfer MJ, Loda M, Mucci LA, Giovannucci E (2011). Vitamin D receptor protein expression in tumor tissue and prostate cancer progression. Journal of Clinical Oncology 29(17):2378-85

Huss L, Butt SM, Borgquist S, Elebro K, Sandsveden M, Rosendahl A & Manjer, J (2019). Vitamin D receptor expression in invasive breast tumors and breast cancer survival. Breast Cancer Research 21(84).

Ke C, Yang F, Wu W, Chung C, Lee R, Yang W, Subeq YM & Liao K (2016). Vitamin D3 Reduces Tissue Damage and Oxidative Stress Caused by Exhaustive Exercise. International Journal of Medical Sciences, 13(2): 147-153.

Köstner K, Denzer N, Müller CS, Klein R, Tilgen W & Jeichrath (2009). The Relevance of Vitamin D Receptor (VDR) Gene Polymorphisms for Cancer: A Review of the Literature. International Journal of AntiCancer Research 29(9): 3511-3536

Rai V, Abdo J, Agrawal S & Agrawal DK (2017). Vitamin D Receptor Polymorphism and Cancer: An Update. Anticancer Treatment International Journal of Cancer Research and Treatment 37(8): 3991-4003

Author:
Fiona Gauci

Reviewers:
Dr. Neville Vassallo
Dr. Christian Zammit

Parkinson's Disease – From Pathogenesis To Novel Therapeutic Approaches

Introduction

Parkinson's Disease (PD) ranks as the second most common neurodegenerative disorder (1). The main site affected is the substantia nigra pars compacta (SNpc) in the midbrain, which suffers a relentless degeneration of dopaminergic neurons of the nigrostriatal pathway, hence resulting in a lack of the neurotransmitter dopamine (DA) in the basal ganglia. Both genetic and environmental factors contribute to the aetiology of the disease (2). Few (10-15%) cases are familial and single gene mutations give rise to less than 5% of PD forms –monogenic (Mendelian inheritance) (3). The genes SNCA, LRRK2 and VPS35, are autosomal dominant, whereas Parkin, PINK1 and DJ-1 are autosomal recessive. Recently, glucocerebrosidase (GBA) gene mutations have been found to be a prime genetic risk factor for PD (4). In fact, heterozygous loss of function of GBA causes more than a five-fold increase in the probability of developing PD (5).

Apart from genetic predisposition, age is a major risk factor for PD. Its incidence climbs up with age to almost 100 per 100,000 person years, between 70 and 79 years (5). The median age of onset is 60 years (5). Substantial evidence shows that a 3:2 ratio of men to women exists (2). In contrast to familial PD, the aetiology of idiopathic PD is multifactorial, as it is the product of an interplay of components: multiple genes, environment and life style -caffeine, smoking and pesticides are among the most strongly associated with PD (3). Moreover, consumption of tea (rich source of polyphenolic compounds), is associated with neuroprotective and neurodegenerative effects in PD, although further studies are needed (6).

Pathophysiology

Since PD involves the extrapyramidal system, this means that the basal ganglia motor circuitry is disturbed (7,8). Since the SNpc projects onto the striatum, the subcortical motor circuitry suffers from loss of DA leading to the motor features accompanying PD.

However, cell degeneration also occurs in other catecholaminergic structures, such as the dorsal nuclei of the vagus and the locus coeruleus, thus explaining the non-motor features of PD (5). DA receptors exist as an excitatory type (D1) and as an inhibitory type (D2).

DA works by affecting motor activity. The basal ganglia are part of this system, namely: striatum substantia nigra pars reticulata (SNpr) and internal globus pallidus (GPi). These structures form part of bigger circuits including the thalamus and the cerebral cortex.
Essentially, two pathways exist: direct (D1) and indirect (D2). The SNpc modulates these pathways by projecting dopamine onto the striatum. DA excites D1 but inhibits D2, and since D2 is in itself inhibitory for (competing) movement, but D1 activates movement, the overall effect of DA is to favour (wanted) motor action. What happens in Parkinson's patients, is that since both pathways are being deprived of dopamine, D1 gets less excited and D2 has its normal inhibition decreased. The outcome is increased inhibitory GPi output, leaving the thalamus with less ability to activate the frontal cortex (9).
Lewy bodies (LB) in the substantia nigra (SN), first identified by Dr. Fritz Heinrich Levi over 100 years ago (10) are a histopathological hallmark of PD (11). These are mainly composed of α-synuclein (α-syn), a presynaptic protein expressed in the brain, which under oxidative stress aggregates. The mechanisms through which LB cause neuron degeneration in the SN are under intense study, and include mitochondrial dysfunction and/or release of pro-apoptotic molecules like cytochrome C (12).

Clinical Features

Although originally described by the English surgeon and apothecary James Parkinson in 1817 as a "shaking palsy" (13), Parkinson's patients experience both motor and non-motor symptoms (NMS). The early stage (around 4-6 years) of the disease comprises non-motor features (Table 1), presenting subtly, and may be easily mistaken as linked to normal aging (2). The crucial triad of motor symptoms are bradykinesia, tremor at rest and muscle rigidity; postural instability is also often a presenting feature. The clinical presentation of PD can vary appreciably between patients. Recognized motor subtypes include: 'postural instability and gait difficulty' (PIGD), 'tremor dominant' and 'indeterminate' (14, 15). A relationship between the patient's age at onset and the PD motor presentations may be present; patients older than 64 years are twice as likely to have tremor at onset compared with patients younger than 45 years (2).
The Unified Parkinson's Disease Rating Scale (UPDRS) is the trusted scale to assess the clinical status of PD patients. Prodromal or premotor symptoms can occur up to 10 years before diagnosis, including: hyposmia, constipation, rapid eye movement sleep behaviour disorder (RBD) and depression. This prodromal

Motor symptoms	Non-motor symptoms
Tremor	Hyposmia
Rigidity	Psychiatric symptoms: depression, anxiety, apathy, hallucinations, psychosis
Bradykinesia	Dementia/cognitive impairment
Postural instability	Sensory symptoms
Postural abnormalities	Genitourinary symptoms: urinary frequency, urgency, reduced libido, sexual dysfunction
Gait disturbances	Gastrointestinal symptoms: constipation, delayed stomach emptying
Alterations in blinking/eye movements	Dysphagia, sialorrhea, dysarthria, hypophonia
Hypomimia	Disturbances of sleep and wakefulness
Micrographia	Cardiovascular symptoms: blood pressure variations, dysrhythmias

Table 1. Motor and Non-motor symptoms of PD. (Adapted from Balestrino & Schapira, 2020).

stage allows identification of those with PD at its primitive stages, a necessity for early treatment (16). A web-based prodromal PD risk calculator which calculates the probability of prodromal PD, has recently become available (17).

Diagnosis

Central to PD diagnosis are a thorough patient's history and physical examination. Over time, the response to treatment and any development of motor fluctuations, must be assessed. Table 2 shows the criteria formalized by the UK Parkinson's Disease Society Brain Bank, with 90% diagnostic accuracy. Early-onset patients have more marked bradykinesia and rigidity, but are less likely to present with gait disturbance than those with late-onset PD (18). Forming an early diagnosis is tied to early identification of non-motor comorbidities, like depression, anosmia, sleep disorders, and their potential association with PD (19).

Imaging techniques, like magnetic resonance imaging (MRI), are useful only to exclude other neurological disorders. Normally, it is only when motor symptoms become prominent that PD is diagnosed, hence the idea of biomarkers may lead to a quicker and earlier diagnosis (2).

Presently, no clinically useful biomarker for PD diagnosis exists. Single-photon emission computed tomography (PET) can be used as dopaminergic imaging to display asymmetric and decreased uptake of striatal dopaminergic biomarkers (particularly in the posterior putamen), suggesting dopaminergic

1. **Bradykinesia and at least one of the following:**	✓ Rigidity ✓ Resting tremor (4-6Hz) ✓ Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction
2. **Exclusion of other causes of parkinsonism**	
3. **At least three of the following supportive (prospective) features:** Unilateral onset, Persistent asymmetry primarily affecting the side of onset, Resting tremor (hand, leg or jaw; low frequency [4–5 Hz], asymmetric, disappears with action), Excellent response to levodopa (70%–100%), Progressive disorder, Severe levodopa-induced chorea (dyskinesias), Levodopa response for five years or more, Clinical course of 10 years or more	

Table 2. Criteria of the UK Parkinson's Disease Society Brain Bank for diagnosing Parkinson disease. (Adapted from Jankovic et al., 2008).

denervation (16). This type of imaging is effective in separating PD from other conditions with no dopaminergic denervation. In the future, 7-T MRI may be useful in assessing the anatomy of the SN (2).

Treatment

Unfortunately, current PD treatment is only symptomatic and primarily targets the dopaminergic pathway. Levodopa (L-dopa) is the cardinal rule for PD treatment –it is the most effectual drug for motor symptoms (20). Whether given in tablet form several times in a day or via duodenal infusion (in advanced disease patients), L-dopa provides a dramatic improvement in symptoms. However, L-dopa brings about peripheral dopaminergic side-effects (can be evaded by decarboxylase inhibitors) and other side-effects like confusion and hallucinations (21). It also causes motor fluctuations and dyskinesia.

These draw-backs may be due to the discontinuous stimulations of dopamine receptors in the striatum, rather than the prolonged dopamine supply (22). The severity of dopaminergic neurodegeneration, the L-dopa dose, low weight and female sex, are all factors linked to the origin of motor complications (23).

Recently, an extended-release carbidopa-levodopa formulation (IPX066) was approved, to decrease motor fluctuations (24). Other formulations like an inhaled formulation and a levodopa prodrug (XP21279) are being investigated (16).

Dopamine agonists trigger the striatal postsynaptic dopamine receptors. Compared to L-dopa, these drugs are less effective in improving the motor symptoms, but are not as likely to cause dyskinesia (16). Monoamine oxidase B (MAO-B) inhibitors reduce dopamine

metabolism and so, extend dopamine stimulation. Since L-dopa is metabolized by Catechol-O-methyl transferase (COMT) enzymes, COMT inhibitors are used as a supplement to L-dopa, since they prolong its half-life (25).

No disease-modifying therapies are available. Hence, the search for potential neuroprotective therapies continues in earnest. Targets for such therapies include: α-syn, calcium homeostasis, mitochondrial dysfunction, oxidative stress and autophagy. Short-interfering RNAs (siRNAs) can be used to decrease α-syn expression (26). Passive and active immunotherapies that target Syn are currently undergoing clinical trials (16). Studies indicate that caffeine and nicotine can affect α-syn aggregation and that isradipine (calcium channel blocker) and urate behave like antioxidants (16). However, isradipine did not show clinical effectiveness in a recent trial (27). The diphenylpyrazole compound, anle138b, has been found to have anti-aggregation effects on α-syn (28). In Tau pathology models (for Alzheimer's disease), anle138b, saved neuronal loss (29), and is undergoing clinical trials.

Drugs that target the GBA pathway are also under investigation (30). Enhancing autophagy can halt the degenerative process of PD, as evidenced in animal and in vitro models (31).

Conclusion

PD pathology is complex, involving an amalgam of genetics, epigenetics and environmental triggers. Despite countless investigations, PD remains incurable. Its complete aetiology is still unknown. Each case is heterogenous and depends on the individual. .

However, our current knowledge of PD is constantly being tested by new discoveries, and should be directed towards the development of biomarkers and disease-modifying measures, if we are to find a cure for this movement disorder, hopefully in the near future.

References

1) Schneider SA, Obeso JA. Clinical and pathological features of Parkinson's disease. Curr Top Behav Neurosci 2015;22:205-220.

2) DeMaagd G, Philip A. Parkinson's Disease and Its Management: Part 1: Disease Entity, Risk Factors, Pathophysiology, Clinical Presentation, and Diagnosis. P T 2015 Aug;40(8):504-532.

3) Kouli A, Torsney KM, Kuan WL. Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. In: Stoker TB, Greenland JC, editors. Parkinson's Disease: Pathogenesis and Clinical Aspects Brisbane (AU); 2018.

4) Riboldi GM, Di Fonzo AB. GBA, Gaucher Disease, and Parkinson's Disease: From Genetic to Clinic to New Therapeutic Approaches. Cells 2019 Apr 19;8(4):364. doi: 10.3390/cells8040364.

5) Lees AJ, Hardy J, Revesz T. Parkinson's Disease. The Lancet. 2009 June;373(9680):2055-2066.

6) Caruana M, Vassallo N. Tea Polyphenols in Parkinson's Disease. Adv Exp Med Biol 2015;863:117-137.

7) chrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. Lancet Neurol 2015 Jan;14(1):57-64.

8) .Chen JJ, Swope DM. Parkinson's disease. In: DiPiro JT, Talbert RL, Yee GC, et al., editors. Pharmacotherapy: A Pathophysiologic Approach. 9th ed. New York, New York: McGraw-Hill; 2014.

9) Purves D, Augustine GJ, Fitzpatrick D, Hall WC, LaMantia A, Mooney, RD, Platt ML, White LE, editors. Neuroscience. 6th ed. Sunderland, Mass: Sinauer Associates, Publishers; 2004.

10) Holdorff, B. Fritz Heinrich Lewy (1885–1950). J Neurol 2006;253(5):677-678.

11) Shults CW. Lewy bodies. Proc Natl Acad Sci U S A 2006 Feb 7;103(6):1661-1668.

12) Ghio S, Camilleri A, Caruana M, Ruf VC, Schmidt F, Leonov A, et al. Cardiolipin Promotes Pore-Forming Activity of Alpha-Synuclein Oligomers in Mitochondrial Membranes. ACS Chem Neurosci 2019 Aug 21;10(8):3815-3829.

3) Parkinson J. An essay on the shaking palsy. London: Sherwood, Neely, and Jones, 1817:1–66.

14) Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 1990 Oct;40(10):1529-1534.

15) Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. Mov Disord 2013 May;28(5):668-670.

16) Balestrino R, Schapira AHV. Parkinson disease. Eur J Neurol 2020 Jan; 27(1):27-42.

17) Heinzel S, Berg D, Gasser T, Chen H, Yao C, Postuma RB, et al. Update of the MDS research criteria for prodromal Parkinson's disease. Mov Disord 2019 Oct;34(10):1464-1470.

18) Gomez Arevalo G, Jorge R, Garcia S, Scipioni O, Gershanik O. Clinical and pharmacological differences in early- versus late-onset Parkinson's disease. Mov Disord 1997 May;12(3):277-284

19) 1.Rizek P, Kumar N, Jog MS. An update on the diagnosis and treatment of Parkinson disease. CMAJ 2016 Nov 1;188(16):1157-1165.

20) 1.Fox SH, Katzenschlager R, Lim SY, Ravina B, Seppi K, Coelho M, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the motor symptoms of Parkinson's disease. Mov Disord 2011 Oct;26 Suppl 3:2.

21) Beaulieu-Boire I, Lang AE. Behavioral effects of levodopa. Mov Disord 2015 Jan;30(1):90-102.

22) Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. Lancet Neurol 2006 Aug;5(8):677-687.

23) Warren Olanow C, Kieburtz K, Rascol O, Poewe W, Schapira AH, Emre M, et al. Factors predictive of the development of Levodopa-induced dyskinesia and wearing-off in Parkinson's disease. Mov Disord 2013 Jul;28(8):1064-1071.

24) Dhall R, Kreitzman DL. Advances in levodopa therapy for Parkinson disease: Review of RYTARY (carbidopa and levodopa) clinical efficacy and safety. Neurology 2016 Apr 5;86(14 Suppl 1):13.

25)Müller T. Catechol-O-methyltransferase inhibitors in Parkinson's disease. Drugs 2015 Feb;75(2):157-174.

26) Alarcón-Arís D, Recasens A, Galofré M, Carballo-Carbajal I, Zacchi N, Ruiz-Bronchal E, et al. Selective α-Synuclein Knockdown in Monoamine Neurons by Intranasal Oligonucleotide Delivery: Potential Therapy for Parkinson's Disease. Mol Ther 2018 Feb 7;26(2):550-567.

27) Simuni T. A phase 3 study of isradipine as a disease-modifying agent in patients with early Parkinson's disease (STEADY-PD III): Final study results. Mov Disord 2019 Sept; 34(Suppl 2).

28) Wagner J, Ryazanov S, Leonov A, Levin J, Shi S, Schmidt F, et al. Anle138b: a novel oligomer modulator for disease-modifying therapy of neurodegenerative diseases such as prion and Parkinson's disease. Acta Neuropathol 2013 Jun;125(6):795-813.

29) 1.Wagner J, Krauss S, Shi S, Ryazanov S, Steffen J, Miklitz C, et al. Reducing tau aggregates with anle138b delays disease progression in a mouse model of tauopathies. Acta Neuropathol 2015 Nov;130(5):619-631.

30)Balestrino R, Schapira AHV. Glucocerebrosidase and Parkinson Disease: Molecular, Clinical, and Therapeutic Implications. Neuroscientist 2018 Oct;24(5):540-559.

31) Moors TE, Hoozemans JJ, Ingrassia A, Beccari T, Parnetti L, Chartier-Harlin MC, et al. Therapeutic potential of autophagy-enhancing agents in Parkinson's disease. Mol Neurodegener 2017 Jan 25;12(1):11-3.

Author:
Gabrielle Grixti

Reviewers:
Prof. Christian Scerri
Dr. James DeGaetano

Does a plant based diet actually decrease the risk of colorectal cancer?

Introduction

Colorectal cancer (CRC) is the third most prevalent cancer (World Cancer Research Fund/American Institute for Cancer Research; Bray et al., 2018) and the second leading cause of cancer mortality worldwide (World Health Organisation).

There are various lifestyle and dietary risk factors for CRC. Diet is the most influential risk factor for CRC other than increasing age, particularly over the age of 50 (Baena & Salinas, 2015); male gender; and genetic predispositions (Brenner et al., 2014). CRC is therefore a threat to public health especially due to increased unhealthy diets rich in meat, processed foods, cholesterol and fat. In fact, CRC incidence is higher in developed countries in comparison with less developed countries (Bishehsari et al., 2014), as studies have shown that a more westernised lifestyle leads to a higher prevalence of CRC (Carroll et al., 2014).

A European study was carried out which involved 347,237 participants who were followed up for 12 years, which led to the conclusion that a decrease in CRC risk can be obtained through the implementation of lifestyle changes such as increased exercise, maintaining a healthy body mass index (BMI), little to no smoking or alcohol intake, and a healthy diet, rich in fibre and low in processed and red meats (Aleksandrova et al., 2014). Implementing various of these lifestyle changes led to the largest decrease in CRC risk.

Meat consumption

Studies show that there is a clear correlation between the prevention of CRC and the implementation of a vegetarian diet (Orlich et al., 2015), as a major variable risk factor for CRC is diet. Most notably a high consumption of red and processed meat are linked to an increased risk (Cross et al., 2007; Norat et al., 2005), whereas a decreased risk is linked to plant foods as they are rich in dietary fiber and nutrients (World Cancer Research Fund/American Institute for Cancer Research, 2011). The International Agency for Research on Cancer has classified processed meats as a Group 1 carcinogen and red meat as a Group 2A carcinogen (International Agency for Research on Cancer; Sobiecki, 2017).

The World Cancer Research Fund/American Institute for Cancer Research stated red and processed meats lead to an increased CRC risk, and therefore one should limit red meat in their diet, and avoid processed meats as much as possible (WCRF/AICR, 2007; WCRF/AICR, 2010). Studies have shown that red and processed meats encourage precancerous lesions to develop in the colons of rats (Pierre et al., 2010; Bastide et al., 2015).

There are various mechanisms which have been studied to explain the relationship between meat and CRC. The mechanisms which seem to be most significant for the development of CRC are: (1) Peptide-derived amines found in processed meats may be N-nitrosated into carcinogenic N-nitroso compounds in the gastrointestinal tract (Bingham et al., 2002); (2) Heme iron from red and processed meats promote CRC due to the cytotoxic effects of heme on epithelial cells (Sesink et al., 1999; Bastide et al., 2012), as well as heme iron acting as a catalyst for both the formation of nitrate compounds and the oxidative degradation of lipids by free radicals which leads to cell injury (Glei et al., 2006); and (3) Mutagenic heterocyclic amines (HCA) are consumed when meat is cooked at high temperatures (Sinha et al., 1998).

The advantages of a vegetarian diet in relation to CRC

Vegetarian diets are also linked to a lower body mass index (BMI), as studies have proven that meat-eaters consume high protein and low fibre, which is associated with an increased BMI (Tonstad et al., 2009). The European Prospective Investigation found that BMI was lowest in vegans, followed by vegetarians, fish eaters, and finally highest in meat-eaters (Spencer et al., 2003). Obesity has been proven to increase the risk of CRC (Baena & Salinas, 2015).

Fruits and vegetables are rich in antioxidants and polyphenols, which have been proven to reduce chronic, cardiovascular and cancer diseases (Vauzour et al., 2010), mainly through their effect on metabolic pathways such as mitogen-activated protein kinase

(MAPK) pathways and cytochrome P450 pathways amongst others (Androutsopoulos et al., 2010). This interplay with metabolic pathways can inhibit the progression of metastatic tumours (Baena & Salinas, 2015).

Plant foods tend to be rich in dietary fiber and nutrients, which protect against CRC, as can be illustrated by Figure 1 below:

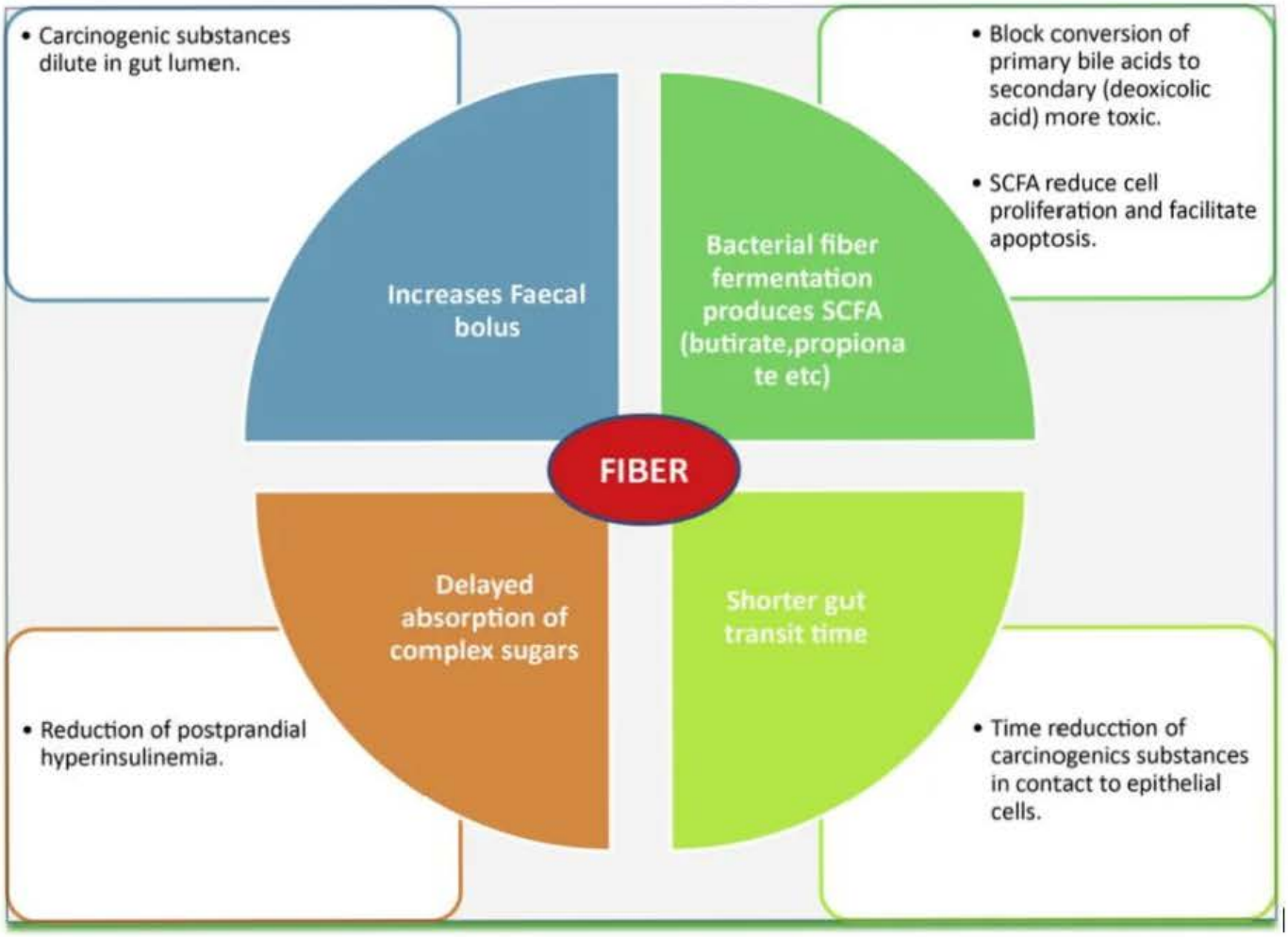

Figure 1. Scheme of potential mechanisms of protection of fiber in colorectal cancer (Baena & Salinas, 2015).

(SCFA = short-chain fatty acids)

Folic acid and CRC

Folic acid, also known as vitamin B9, can be obtained naturally in one's diet from foods such as broccoli, leafy green vegetables, kidney beans and fortified breakfast cereals, and has been shown to reduce the risk of CRC (Tárraga López et al., 2013). However, when folic acid is obtained from folic acid supplements and exceeds the daily recommended dose of 1000 µg/day, it may increase the risk of neoplasms (Durko & Malecka-Panas, 2014).

What about pescovegetarians?

Research has however shown that a moderate amount of fish may provide some protection against developing CRC (Baena & Salinas, 2015), as fish contain high amounts of vitamin D and omega-3 fatty acids (Vargas & Thompson, 2012). High vitamin D intake has been linked to a decreased risk for various types of cancer. Various epidemiological studies have proven that Vitamin D offers a direct protective role on CRC (Garland & Garland, 1980; Byers et al., 2012) and on the contrary, low levels of Vitamin D have been linked to increased risk of CRC (Jenab et al., 2010). Fish are primary sources of n-3 long chain polyunsaturated fatty acids (n-3 LC-PUFAs) (Delarue et al., 2004). Research shows that n-3 LC-PUFAs produce anti-inflammatory eicosanoids which may inhibit tumour development (DiNicolantonio & O'Keefe, 2018).

Individuals who incorporated fish into their diet exhibited approximately a 10% reduced risk for CRC (Aglago et al., 2019).

A major study published in the Journal of the American Medical Association, called the Adventist Health Study 2 (AHS-2) involved 96,354 Adventist North Americans who were followed up for 7.3 years. This study concluded that overall meat-eaters showed an increased frequency of CRC, and most notably pescovegetarians (vegetarians who include fish in their diet) had the largest decrease in CRC risk (Orlich et al., 2015).

In spite of these studies, the World Cancer Research Fund analysed various studies and concluded that evidence that fish reduces the risk for CRC is "limited but suggestive," so there is still certain uncertainty whether implementing fish into one's diet prevents CRC (World Cancer Research Fund/American Institute for Cancer Research, 2018; Aglago et al., 2019).

The effects of alcohol and smoking on CRC

Alcohol can also directly affect one's risk for CRC, as when ethanol is metabolised, acetaldehyde is produced, which is carcinogenic and may lead to CRC development (Reidy et al., 2011). There is a 16% increase in CRC risk associated with 30g/day of alcohol intake, and a 41% increase in risk associated with a 45g/day intake (Durko & Malecka-Panas,

2014), indicating that the risk for CRC increases with increasing alcohol intake (Tárraga López et al., 2013). This correlation is observed less frequently in females than in males (Baena & Salinas, 2015).

Smoking is another well known carcinogen which is associated with CRC. Studies show that non-smokers have an increased survival rate when compared to smokers (Zhu et al., 2014). Therefore there is a clear dose-response relationship between smoking and CRC outcome (Phipps et al., 2013; Walter et al., 2015).

Conclusion

CRC incidence is steadily increasing, especially due to the fact that more countries are adopting a more westernised lifestyle. Studies have shown there is a direct link between high consumption of red and processed meat and CRC, as these foods are carcinogenic. Therefore, the implementation of a vegetarian diet may lead to a decrease in CRC risk, especially since plant foods are rich in antioxidants, polyphenols, dietary fiber and nutrients such as folic acid, which are all protective factors against CRC. Pescovegetarians also seem to have a further decreased risk of CRC, notably due to the fact that fish contain high amounts of vitamin D, which plays an active role in immunity and has a protective role against various types of cancers. Other than these major dietary risk factors, alcohol and smoking are among other major links attributed with CRC, so eliminating these from one's lifestyle further helps to decrease their risk of CRC.

References

Aglago EK, Huybrechts I, Murphy N, et al. (2020). Consumption of Fish and Long-chain n-3 Polyunsaturated Fatty Acids Is Associated With Reduced Risk of Colorectal Cancer in a Large European Cohort. Clin Gastroenterol Hepatol. 18(3):654-666.e6. doi:10.1016/j.cgh.2019.06.031

Aleksandrova, K., Pischon, T., Jenab, M. et al. (2014). Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. BMC Med 12, 168. https://doi.org/10.1186/s12916-014-0168-4

Androutsopoulos V.P., Papakyriakou A., Vourloumis D., Tsatsakis A.M., Spandidos D.A. (2010). Dietary flavonoids in cáncer therapy and prevention: Substrates and inhibitors of cytochrome P450 CYP1 enzymes. Pharmacol Therapeut, 126 , pp. 9-20

Baena R.; Salinas P. (2015). Diet and Colorectal Cancer. Maturitas 80.3: 258-64.

Bastide NM, Chenni F, Audebert M, et al. (2015). A central role for heme iron in colon carcinogenesis associated with red meat intake. Cancer Res. 75(5):870-879. doi:10.1158/0008-5472.CAN-14-2554

Bastide NM, Pierre FH, Corpet DE. (2012). Heme iron from meat and risk of colorectal cancer: a meta-analysis and a review of the mechanisms involved. Cancer Prev Res (Phila); 4:177–84.

BinghamSA, Hughes R, Cross AJ. (2002). Effect of white versus red meat on endogenous N-nitrosation in the human colon and further evidence of a dose response. J Nutr; 132:3522S–5S.

Bishehsari, F., Mahdavinia, M., Vacca, M., Malekzadeh, R., & Mariani-Costantini, R. (2014). Epidemiological transition of colorectal cancer in developing countries: environmental factors, molecular pathways, and opportunities for prevention. World journal of gastroenterology, 20(20), 6055–6072. https://doi.org/10.3748/wjg.v20.i20.6055

Bray F., Ferlay J., Soerjomataram I. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin.; 68: 394-424

Brenner H, Kloor M, Pox C.P. (2014). Colorectal cancer. Lancet, 383, pp. 1490-1502

Byers, S. W., Rowlands, T., Beildeck, M., and Bong, Y. S. (2012). Mechanism of action of vitamin D and the vitamin D receptor in colorectal cancer prevention and treatment. Rev. Endocr. Metab. Disord. 13, 31–38.

Byers, S. W., Rowlands, T., Beildeck, M., and Bong, Y. S. (2012). Mechanism of action of vitamin D and the vitamin D receptor in colorectal cancer prevention and treatment. Rev. Endocr. Metab. Disord. 13, 31–38.

Orlich, M. J., Singh, P. N., Sabaté, J., Fan, J., Sveen, L., Bennett, H., Knutsen, S. F., Beeson, W. L., Jaceldo-Siegl, K., Butler, T. L., Herring, R. P., & Fraser, G. E. (2015). Vegetarian dietary patterns and the risk of colorectal cancers. JAMA internal medicine, 175(5), 767–776. https://doi.org/10.1001/jamainternmed.2015.59

Perera P.S., Thompson R.L., Weseman M.J. (2012). Recent evidence for colorectal cancer prevention through healthy food, nutrition, and physical activity: implications for recommendations. Curr Nutr Rep, 1, pp. 44-54

Pérez-Cueto F.J.A., Wim Verbeke W. (2012). Consumer implications of de WCRF's permanent update on colorectal cancer. Meat Sci, 90, pp. 977-978

Phipps AI, Shi Q, Newcomb PA, et al. (2013). Associations between cigarette smoking status and colon cancer prognosis among participants in north central cancer treatment group phase III trial n0147. J Clin Oncol; 31: 2016–23.

PierreFH, Santarelli RL, Allam O, TacheS, Naud N, Gueraud F, et al. (2010). Freeze-dried ham promotes azoxymethane-induced mucin-depleted foci and aberrant crypt foci in rat colon. Nutr Cancer; 62:567–73.

Reidy J., McHugh E., Stassen L.F.A. (2011). A review of the relationship between alcohol and oral cancer. Surgeon, 9, pp. 278-283

Sesink ALA, Termont DSML, Kleibeuker JH, Vandermeer R. (1999). Red meat and colon cancer: the cytotoxic and hyperproliferative effects of dietary heme. Cancer Res; 59:5704–9.

SinhaR, Knize MG, Salmon CP, BrownED, Rhodes D, Felton JS, et al. (1998). Heterocyclic amine content of pork products cooked by different methods and to varying degrees of doneness. Food Chem Toxicol;36:289–97.

Sobiecki J. G. (2017). Vegetarianism and colorectal cancer risk in a low-selenium environment: effect modification by selenium status? A possible factor contributing to the null results in British vegetarians. European journal of nutrition, 56(5), 1819–1832. https://doi.org/10.1007/s00394-016-1364-0

Spencer EA, Appleby PN, Davey GK, Key TJ. (2003). Diet and body mass index in 38000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians and vegans. Int J Obes Relat Metab Disord.;27(6):728–734.

Tonstad S, Butler T, Yan R, Fraser GE. (2009). Type of vegetarian diet, body weight, and prevalence of type 2 diabetes. Diabetes Care.;32(5):791–796.

Vargas A.J., Thompson P.A. (2012). Diet and nutrient factors in colorectal cancer risk. Nutr Clin Pract, 27 (5), pp. 613-623

Vauzour D., Rodriguez-Mateos A., Corona G., Oruna-Concha M.J., Spencer J.P.E. (2010). Polyphenols and human health: prevention of disease and mechanisms of action. Nutrients, 2, pp. 1106-1131

Walter V, Jansen L, Hoffmeister M, Ulrich A, Chang-Claude J, Brenner H. (2015). Smoking and survival of colorectal cancer patients: population-based study from Germany. Int J Cancer;137(6):1433-1445. doi:10.1002/ijc.29511

World Cancer Research Fund/American Institute for Cancer Research (2018). Colorectal cancer statistics. https://www.wcrf.org/dietandcancer/cancer-trends/colorectal-cancer-statistics

World Cancer Research Fund/American Institute for Cancer Research (2011). Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer. http://www.wcrf.org/sites/default/files/Colorectal-Cancer-2011-Report.pdf

World Cancer Research Fund/American Institute for Cancer Research (2007). Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington DC: WCRF and American Institute for Cancer Research;. p. 1–537.

World Cancer Research Fund/American Institute for Cancer Research (2010). Systematic Literature Review Continuous Update Project Report: The associations between food, nutrition and physical activity and the risk of colorectal cancer. Washington DC:WCRF and American Institute for Cancer Research; p. 1–855.

World Health Organization (2018) https://www.who.int/news-room/fact-sheets/detail/cancer

Zhu Y, Yang SR, Wang PP, et al. (2014). Influence of pre-diagnostic cigarette smoking on colorectal cancer survival: overall and by tumour molecular phenotype. Br J Cancer; 110: 1359– 66.

Author:
Matteo Galea

Reviewer:
Dr. Christian Zammit

Phantom Limb Syndrome: A Review

Introduction

Phantom limb syndrome is a condition whereby patients experience painful or non-painful, kinaesthetic sensory sensations in a non-existing limb. French surgeon Ambroise Paré was the first to observe this phenomenon in 1551, after critically wounded soldiers had to undergo subsequent limb amputation.1,2 An approximate 98% and up to 80% of amputees experience phantom limb sensations (PLS) and phantom limb pain (PLP) respectively.3,4 This literature review will primarily focus on the pathophysiology of phantom limb syndrome, its clinical manifestation and PLP management. Despite its prevalence, phantom limb syndrome is still regarded as a poorly understood phenomenon making it a chronic syndrome particularly difficult to treat.

Pathophysiology

The "body schema" provides a general framework and serves as a basis for its underlying pathophysiological mechanism. It can be broadly defined as an ongoing dynamic and evolving bodily experience whereby combined 'visual', 'motor' and 'proprioceptive' feedback information generate a single, integrated perception of oneself. Pathological states may potentially influence this combined self-perception leading to disorders of spatial perception as may occur as a result of limb nerve deafferentation and amputation.5,6 With an amputated limb, the brain receives solely proprioceptive information regarding its location rather than combined visual-proprioception feedback.

This dissociation might cause the brain to conjure up a phantom limb (PL).7 The perception of PL movement may in turn occur due to mirror neurons which potentially play a pivotal role both in the 'body schema' and hence in PLS. These mirror neurons allow one to mimic other people's bodily movement through simple observation by activating the observer's own muscles involved in the perceived action.8 Melzack's neuromatrix theory further explores this notion of the "body schema" and hypothesizes that pain is a

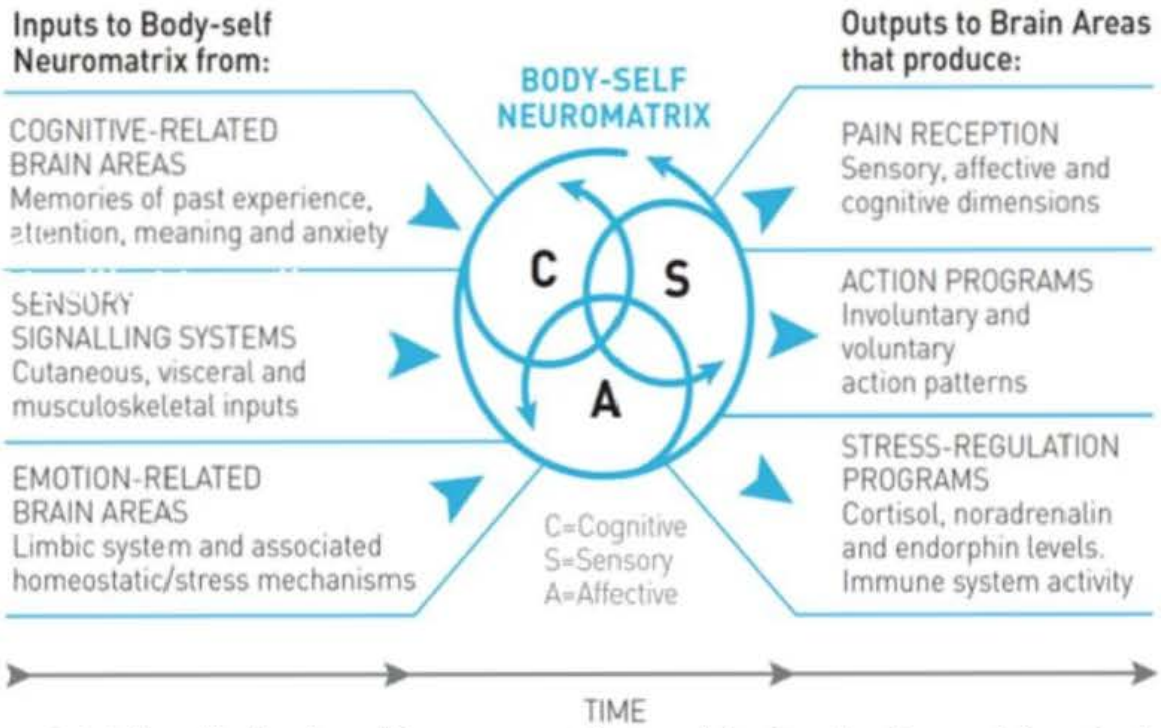

Figure 1: Melzack's body-self neuromatrix model of pain. Several input signals to the brain may trigger a pain neurosignature including cognitive, sensory and limbic feedback information. Pain is ultimately an output of the brain brought about by the activation of neurosignatures and regardless of any sensory input.11

complex experience brought about by the modulation and triggering of 'neurosignatures'(Figure 1).9,10

Neurosignatures are pattern characteristics in the neuromatrix which are generated through repeated "cyclical processing and synthesis of nerve impulses". Apart from being triggered through perceptual inputs affecting the thalamocorticol, somatosensory and limbic systems, they can also be self-generating in the absence of any input signals from the body.11,12 This correlates with the pain memory hypothesis which states that pain experienced by patients prior to subsequent amputation is stored in one's memory, thus being an important trigger for eliciting phantom pain even in the absence of any peripheral stimulation.13

Similarly, these pain memories play a fundamental role in 'empathic pain' which may elicit PLP by simply acknowledging, thinking or inferring an observed person in pain.10

Despite these theories suggesting a common etiology for both PLS and PLP, several studies have observed that phantom pain relief does not alter phantom sensations and vice versa.14 This suggests that there may be more underlying pathophysiological mechanisms for eliciting PLP.

Patients suffering from anxiety, stress, depression and poor coping mechanisms are more likely to experience PLP. However, the psyche should not be regarded as a primary elicitor.15 In fact, the peripheral system

is undoubtedly involved as it has been observed that the frequency of PLP is higher amongst patients suffering from stump pain. This most likely arises from neuromas at the nerve transection site due to increased ectopic firing of the A and C fibers. Despite this, patients may still experience PLP even in the absence of stump pain.16

The central nervous system also plays a prominent role in PLP. Unregulated activity of peripheral nociceptors at amputation site induces plasticity of dorsal horn neurons resulting in central sensitization. These neurons eventually become damaged generating pain impulses.17 Similarly, peripheral nerve damage may trigger central hyperexcitability resulting in spinal cord reorganization (Figure 2).18 Moreover, Flor et al. observed that cortical reorganization and PLP development were found to be directly proportional, suggesting that supraspinal changes may play a prominent role in PLP.19 Cortical remapping has also been attributed to telescoping of the limb, whereby the cortex remaps the distal limb portion onto adjacent areas e.g. shoulder. This causes amputee patients to perceive the phantom limb as being shortened such that the distal portion of the missing limb is closer to the stump and appears to be magnified. 3,10,15

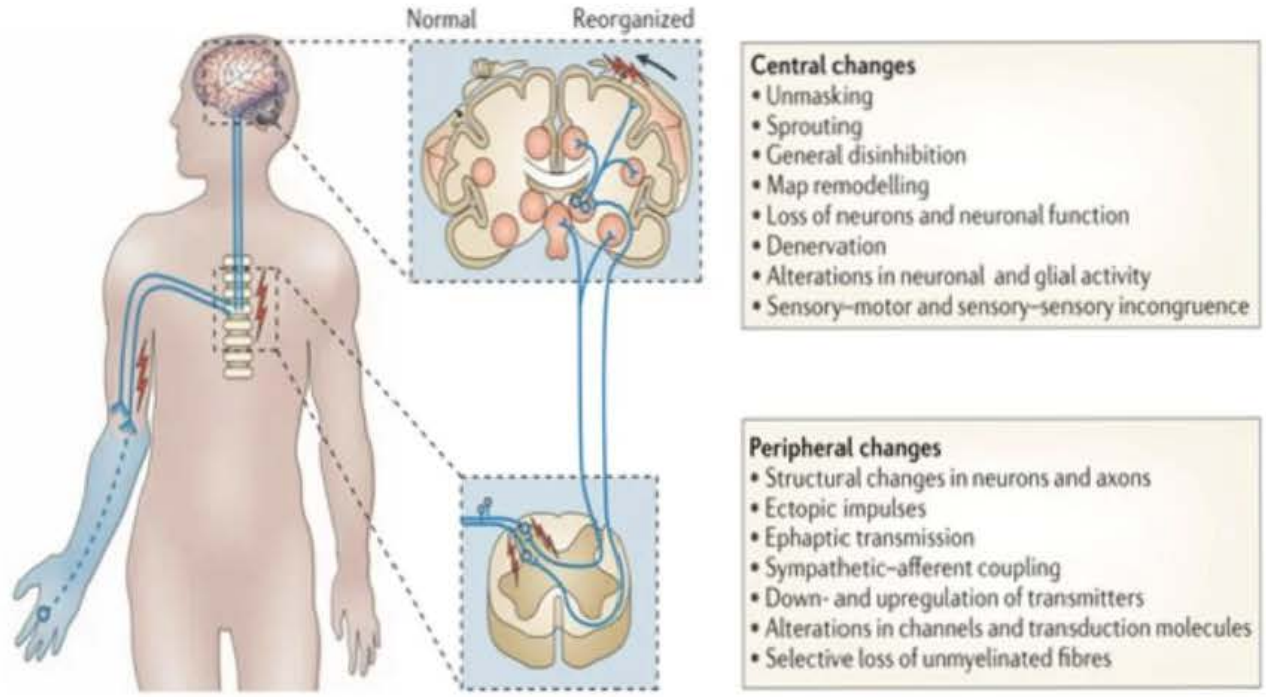

Figure 2: Central and peripheral changes occurring in PLP. Peripheral areas include the residual limb and dorsal root ganglion whilst the central areas include the spinal cord and the supraspinal centres namely the cortex, thalamus, brainstem and limbic system.18

Evaluation

Diagnosing PLP is somewhat difficult. Care must be taken to try and differentiate PLP from residual limb pain (RLP) as these are treated differently. Careful examination is required, both of skin tissue at amputation site so as to exclude infection/wounds as well as the joint above, to check for any signs of joint dysfunction. Sensations tests are also carried out and pain intensity is assessed. RLP is usually mild compared to PLP, the latter of which is often described as being intermittent with burning, throbbing/tingling, cramping or shooting sensations. Indeed, PLP diagnosis is often a 'diagnosis of exclusion' and heavily reliant on the patient's history.20

Treatment

The complexity of PLP combined with the fact that much of its pathophysiology stills remains uncertain, makes it a chronic syndrome which is arduous to treat. Various treatment options exist including pharmacological, non-pharmacological and invasive treatments. However, the treatment plan offered to the patient is mainly based upon the severity of pain being experienced (Table 1).21

Table 1: Overview of Treatment Modalities for PLP.21

PHARMACOLOGICAL	NONINVASIVE	INVASIVE
NSAIDS	**Mirror Therapy**	**Neurectomy**
Acetaminophen	**Transcutaneous Electrical Nerve Stimulation (TENS)**	**Dorsal Root End Zone (DREZ) lesion**
Opioids: Morphine Tramadol Methodone	**Biofeedback**	**Cordotomy**
	Relaxation Technique	**Thalamotomy**
Antidepressants: TCAs SNRIs	**Hypnosis**	**Sympathectomy**
	Acupuncture	**Spinal cord stimulation**
Anticonvulsants: Gabapentin Carbamazepine Topiramate		**Deep brain stimulation**
NMDA receptor antagonists: Ketamine Memantine		
Calcitonin		

Pharmacological Treatment

Pharmacotherapy is generally regarded as the first-line treatment modality. The most commonly prescribed drugs for providing moderate pain relief include non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen.22 Anticonvulsant drugs such as gabapentin may also prove useful to tone down neuropathic pain intensity and frequency.

However, similar to antidepressants as well as calcitonin, their effect on PLP has still been not confirmed as reports from various clinical trials have been inconsistent in their findings.21 Opioids and opiates may prove to be a suitable alternative and are often prescribed for neuropathic pain relief.

These perhaps represent the most effective type of pharmacological treatment for short-term relief, despite their negative connotation with drug dependence and the commonly reported side-effects such as constipation, sedation and nausea. Indeed, studies have reported a significant reduction in PLP both with oral and intravenous administration of morphine.23,24 It has been hypothesized that a contributing factor for opioid efficacy lies in their ability to disrupt cortisol reorganization, considered to be one of the main contributing factors for the pathophysiology of PLP. Despite this, available studies have not assessed whether morphine is effective in providing long term pain relief.24,25 On the other hand, intravenous administration N-methy-D-Aspartate (NMDA) receptor antagonist, namely ketamine, proved to be highly effective in reducing PLP incidence and potentially complete resolution.26 Nevertheless, these observations were mainly reported when such drugs were given intravenously. In fact, Maier et al. reported no significant clinical benefits in alleviating chronic PLP through oral administration of memantine.27

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Non-Invasive treatment

Mirror therapy (MT) is proving to be a pioneer in providing PLP relief both in terms of cost and efficacy, with one study even reporting a 93% decrease in pain intensity.28 It consists of a parasagittally placed mirror between the upper/lower limb. The patient then moves the unaffected limb whilst observing its reflection in the mirror.

At the same time, they try to mimic the perceived movement in the reflection using their phantom limb. Thus, the virtual limb takes the role of the amputated limb. It has been hypothesized that the basis of MT lies in the dampening of the distorted perception between visual and proprioceptive feedback. This concept of MT has also recently taken a step forward via virtual reality proving a more avant-garde perspective in alleviating PLP.16 Another form of non-invasive procedure is transcutaneous electrical nerve stimulation (TENS) which is also proving to be a promising treatment modality. TENS employs the use of skin electrodes to transmit a mild electric current to cutaneous nerve fibers. A reported average decrease of 66% in PLP has been reported and may provide a temporary relief of PLP for up to one year.29

Invasive treatment

Invasive treatment is generally avoided and is associated with high recurrence rates and high risks for permanent nerve damage apart, apart from providing only short-term relief. Such procedures may include neuroablative neuroma resection, anterolateral cordotomy and sympathectomy amongst others. These are regarded as the last resort and before patients are referred to surgical intervention, it is ensured that conservative treatment modalities have been thoroughly exhausted without any clinical success.21

Conclusion

The exact underlying pathophysiology of phantom limb syndrome together with the potential manifestation of PLP, are complex mechanisms which despite their prevalence, remain elusive. Some promising therapies have been proposed throughout the years, most notably the use of MT and virtual reality. However, further research is required. Most of the current treatment options offered are rather of low quality. Indeed, the best treatment modality for management ultimately lies in unlocking the underlying pathophysiological mechanisms for their clinical manifestation.

References

1.Chahine L, Kanazi G. Phantom limb syndrome: a review. Middle East J Anaesthesiol. 2007;19(2):345-355.

2.Keil G. Sogenannte Erstbeschreibung des Phantomschmerzes von Ambroise Paré. "Chose digne d'admiration et quasi incredible": die "douleur ès parties mortes et amputées" [So-called initial description of phantom pain by Ambroise Paré. "Chose digne d'admiration et quasi incredible": the "douleur ès parties mortes et amputées"]. Fortschr Med. 1990;108(4):62-66.

3.Ramachandran VS, Hirstein W. The perception of phantom limbs. The D. O. Hebb lecture. Brain. 1998;121 (Pt 9):1603-1630.

4.Kooijman CM, Dijkstra PU, Geertzen JH, Elzinga A, van der Schans CP. Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. Pain. 2000;87(1):33-41.

5.McGonigle DJ, Hänninen R, Salenius S, Hari R, Frackowiak RS, Frith CD. Whose arm is it anyway? An fMRI case study of supernumerary phantom limb. Brain. 2002;125 (Pt 6):1265-1274.

6.Vallar G. Spatial frames of reference and somatosensory processing: a neuropsychological perspective. Philos Trans R Soc Lond B Biol Sci. 1997;352(1360):1401-1409.

7.Collins KL, Russell HG, Schumacher PJ, et al. A review of current theories and treatments for phantom limb pain. J Clin Invest. 2018;128(6):2168-2176.

8.Fadiga L, Craighero L, Olivier E. Human motor cortex excitability during the perception of others' action. Curr Opin Neurobiol. 2005;15(2):213-218.

9.Melzack R. From the gate to the neuromatrix. Pain. 1999;Suppl 6:S121-S126.

10.Giummarra MJ, Gibson SJ, Georgiou-Karistianis N, Bradshaw JL. Central mechanisms in phantom limb perception: the past, present and future. Brain Res Rev. 2007;54(1):219-232.

11.Melzack R. Pain and the neuromatrix in the brain. J Dent Educ. 2001;65(12):1378-1382.

12.Melzack R. The gate control theory 25 years later: new perspectives on phantom limb pain. In: Bond MR, Charlton JE, Woolf CJ. Pain research and therapy: Proceedings of the VIth World Congress on Pain. Amsterdam: Elsevier, 1991:9-26.

13.Flor H. Phantom-limb pain: characteristics, causes, and treatment. Lancet Neurol. 2002;1(3):182-189.

14.Davis RW. Phantom sensation, phantom pain, and stump pain. Arch Phys Med Rehabil. 1993;74(1):79-91.

15.Flor H, Nikolajsen L, Staehelin Jensen T. Phantom limb pain: a case of maladaptive CNS plasticity?. Nat Rev Neurosci. 2006;7(11):873-881.

16.Weeks SR, Anderson-Barnes VC, Tsao JW. Phantom limb pain: theories and therapies. Neurologist. 2010;16(5):277-286.

17.Woolf, C. J. & Salter, M. W. in Wall and Melzack's Textbook of Pain (eds Koltzenburg, M. & McMahon, S. B.) 91–105 (Elsevier, Amsterdam, 2005).

18.Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. Life Sci. 2004;74(21):2605-2610.

19.Flor H, Elbert T, Mühlnickel W, Pantev C, Wienbruch C, Taub E. Cortical reorganization and phantom phenomena in congenital and traumatic upper-extremity amputees. Exp Brain Res. 1998;119(2):205-212.

20.Hanyu-Deutmeyer AA, Cascella M, Varacallo M. Phantom Limb Pain. In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 4, 2020.

21.Luo Y, Anderson TA. Phantom Limb Pain: A Review. Int Anesthesiol Clin. 2016;54(2):121-139.

22.Hanley MA, Ehde DM, Campbell KM, Osborn B, Smith DG. Self-reported treatments used for lower-limb phantom pain: descriptive findings. Arch Phys Med Rehabil. 2006;87(2):270-277.

23.Wu CL, Tella P, Staats PS, et al. Analgesic effects of intravenous lidocaine and morphine on postamputation pain: a randomized double-blind, active placebo-controlled, crossover trial. Anesthesiology. 2002;96(4):841-848.

24.Wu CL, Agarwal S, Tella PK, et al. Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. Anesthesiology. 2008;109(2):289-296.

25.Huse E, Larbig W, Flor H, Birbaumer N. The effect of opioids on phantom limb pain and cortical reorganization. Pain. 2001;90(1-2):47-55.

26.Nikolajsen L, Hansen CL, Nielsen J, Keller J, Arendt-Nielsen L, Jensen TS. The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input. Pain. 1996;67(1):69-77.

27.Maier C, Dertwinkel R, Mansourian N, et al. Efficacy of the NMDA-receptor antagonist memantine in patients with chronic phantom limb pain--results of a randomized double-blinded, placebo-controlled trial. Pain. 2003;103(3):277-283.

28.Chan BL, Witt R, Charrow AP, et al. Mirror therapy for phantom limb pain. N Engl J Med. 2007;357(21):2206-2207.

29.Melzack R. Prolonged relief of pain by brief, intense transcutaneous somatic stimulation. Pain. 1975;1(4):357-373.

Case Report

Author:
Mark Miruzzi

Reviewer:
Dr. Maria Mallia
Dr. Pierre Mallia

Frontotemporal Dementia

Introduction

Frontotemporal dementia (FTD) is a neurodegenerative disorder of insidious onset, and the term encompasses several entities. It is mostly sporadic. Epidemiologically, its prevalence as a dementia is third behind Alzheimer's disease and dementia with Lewy bodies (Bang et al., 2018). The incidence of FTD is around 1.61-4.1 cases per 100,000 people annually (Coyle-Gilchrist et al., 2016), and the most common age of onset is in the sixth decade (Kelley and El-Khouri, 2016). This case report highlights the fact that the presentation of frontotemporal dementia can be subtle, and can present a diagnostic difficulty when differentiating it from vascular dementia and other cognitive disorders.

Case Presentation

Mr AF is a 72-year-old gentleman, former businessman who lives with his wife. He first presented to the Neurology Cognitive clinic on 04/04/2019 in view of a history of forgetfulness of unclear onset; one of the main complaints that most bothered the patient was that he could not remember where he had parked his car. Appropriate workup was done, and the clinical impression was that of mild cognitive impairment with insidious onset.

There were subtle changes in his behaviour, but no motor symptoms and no gait disturbance. His sleeping habits had not changed recently (he sleeps at 2am and wakes up at 7am), no weight loss was reported and there were no problems with continence. His wife stated that his initiative-taking was unchanged. There was no history of hallucinations, insight was retained and he was independent in daily life.

His functional status was assessed: he was managing all activities of daily living. He was still driving, but required someone to guide him regarding road directions. His wife stated that he did not drive dangerously and his difficulty in directions had always been present. The patient was still involved in some family business once a week.

The patient is the patient is healthy enough to perform activities of daily living but has a number of cardiovascular risk factors. He is a known case of hypercholesterolaemia

and diabetes mellitus, and has been hospitalised with compressive chest pain suggestive of angina pectoris. The patient experiences exertional dyspnoea on walking up hills, and also reported GI symptoms such as dyspepsia and occasional abdominal pain

As shown in figure 1, the patient was admitted with abdominal pain and had a colonoscopy on 09/09/2010. This showed diverticulosis, mainly in the sigmoid colon.

The patient had other comorbidities: on 31/08/2017, an MRI of the lumbar/sacral spine was performed in view of clinical findings suggestive of S1 radiculopathy: degenerative disc change was seen throughout the thoracolumbar spine, most prominent at the L4/5 and L5/S1 levels, contributing to severe vertebral canal stenosis at the L4/5 level. The patient also required a shoulder operation for severe stiffness and reduced joint mobility, which was performed on 29/11/2016.

Table 1 summarises the patient's drug history and allergies.

When assessing a neurocognitive disorder, it is important to ask for any family history of similar problems. The patient doesn't have any first-degree relatives who suffer from dementia. The patient has some family members who also suffer from hypertension, diabetes and hypercholesterolaemia The patient is a former businessman who still does

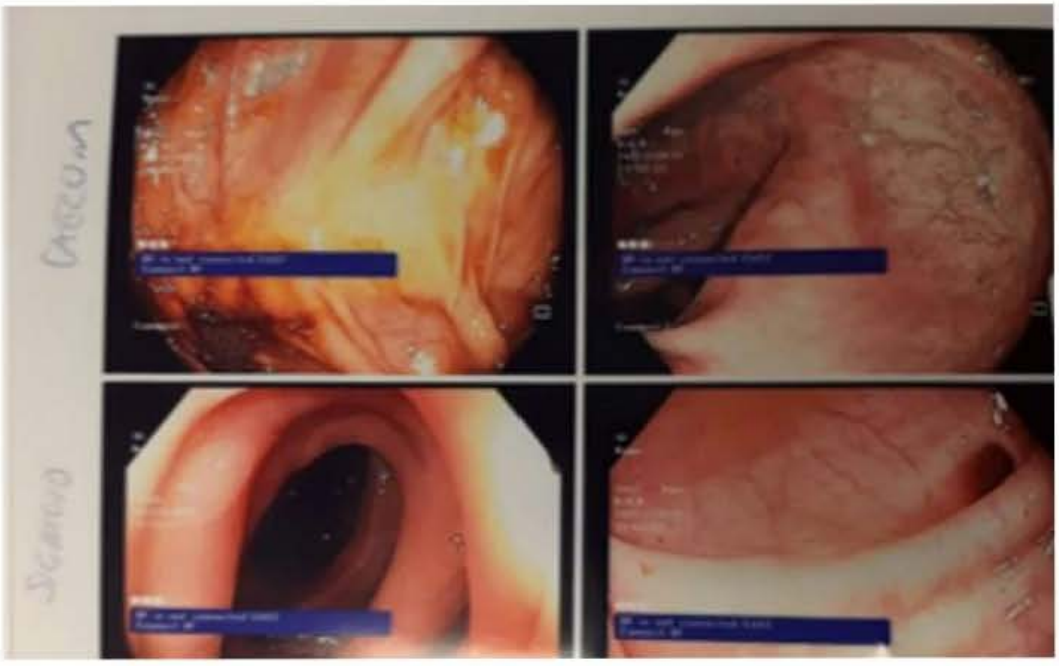

Figure 1:
Family Pedigree (Tazen et al., 2013). The proband – female with SCA2 with an unaffected mother and a deceased unaffected father, having CAG repeat expansions in ATXN2 . The paternal deceased uncle had ALS with the same trinucleotide repeat expansion as the proband but with different lengths.

Medication	Dose	Reason for taking Medication
Aspirin	75mg PO once daily	Ischaemic heart disease
Clopidogrel	75mg PO once daily	Ischaemic heart disease
Simvastatin	40mg PO nocte	Hypercholesterolaemia
Tamsulosin	1 tab daily	Benign prostatic hyperplasia

Table 1: Mr A.F.'s current medications. No known drug allergies

some family business affairs. He was a smoker from age 16 to 56, and only consumes alcohol socially.

On examination, respiratory rate was normal, SpO2 98% on room air, temperature 36.8oC, blood pressure 157/84mmHg, pulse 73 bpm. Neurocognitive testing showed that Mr A.F. was euthymic, with no difficulties with language comprehension or expression. The examination findings are summarised in table 2.

When formulating a differential diagnosis for such a case, one had to keep in mind that the clinical presentation of FTD is initially quite vague, so a number of neurological and psychiatric pathologies were considered:

1.Alzheimer disease (commonest cause of cognitive impairment)
2.Vascular dementia (multiple risk factors)
3.Schizophrenic personality disorder (psychiatric manifestations)
4.Dementia with Lewy bodies (unlikely)
5.Normal pressure hydrocephalus (cognitive impairment but no gait or urinary issues)
6.Benign/malignant brain tumour (change in personality)

Differentiating FTD from the other common cause of cognitive decline (Alzheimer's disease) and ruling out vascular causes is challenging because of overlapping symptoms and clinical features. FTD was the initial diagnosis in this patient, presenting mainly with behavioural changes and change in

Visuospatial Assessment	Normal except difficulties copying a cube (three-dimensionality not correct)
Attention: Serial 7s	4/5
Registration	Full marks
MMSE	Difficulties with recall
Clock Test	4/5, both hands drawn equally
Naming	Could not name 'penguin' and 'anchor'
Verbal Fluency	10 words starting with P in one minute
Three-stage command	Good
Sentence-writing	Good, except no question mark at the end
Antegrade memory	7/7
Episodic memory	Good
Attention	Serial subtraction 4/5

Table 2: Examination findings

affect. This was shown by his lack of spontaneous speech, coming through as apathetic, despite his preserved language ability. Although he had mild naming difficulties, Mr AF did well in verbal fluency tests, comprehension and writing. It would be interesting to check performance on tasks of facial expression recognition, as these patients typically do poorly.

Vascular dementia is typically characterised by a stepwise decline, particularly in executive functions. In contrast, Alzheimer's disease and FTD show a progressive course, mainly in episodic memory. Imaging techniques are useful in order to identify affected brain regions. Atrophy or hypometabolism of the right frontal or right temporal lobe is the hallmark neuroimaging finding in patients with bvFTD. When both frontal lobes are involved, language symptoms are typically also present.

A strictly vascular dementia in this case was less likely but could not be excluded. Mixed dementia is a dementia where both vascular lesions and other pathology co-exist to produce cognitive impairment. Demented patients have a greater incidence of stroke and stroke patients have a greater incidence of dementia (Leys et al, 2005).

Diagnostic investigations:

Investigation: blood investigations: complete blood count, renal profile, lipid profile
Justification: this patient has a history of prior admission with neutropenia, and he has multiple comorbidities which may result in anaemia of chronic disease. Renal profile helps to assess kidney perfusion in this patient with heart disease and other risk factors for chronic kidney disease. The lipid profile is important since the patient has hypercholesterolaemia
Result & conclusion: leukopenia (followed up by haematologist), normal U&E and creatinine, elevated LDL and total cholesterol

Investigation: nuclear medicine positron emission tomography (NM-PET/CT) brain
Justification: identify areas of the brain that are affected by the pathology, and help differentiate from conditions such as Alzheimer's disease.
Result & conclusion: decreased uptake in the left parieto-temporal cortex and the left posterior cingulate cortex. FDG-PET imaging showed non-specific changes, which helped the diagnosis veer away from Alzheimer's pathology.

Investigation: electroencephalogram (EEG)
Justification: forgetfulness, look for encephalopathic changes/ focal abnormalities
Result & conclusion: figure 2: the patient's EEG is abnormal and showed generalised non-specific slowing, symmetrical, so this was non-specific and did not help in the differential diagnosis. The generalised slow wave activity is consistent with a non-specific encephalopathy. There are no focal or epileptiform features. The background consists mainly of alpha rhythm at 8-9c/sec of medium amplitude (20-30μV) intermixed with theta activity at 6c/second over both hemispheres in the background.

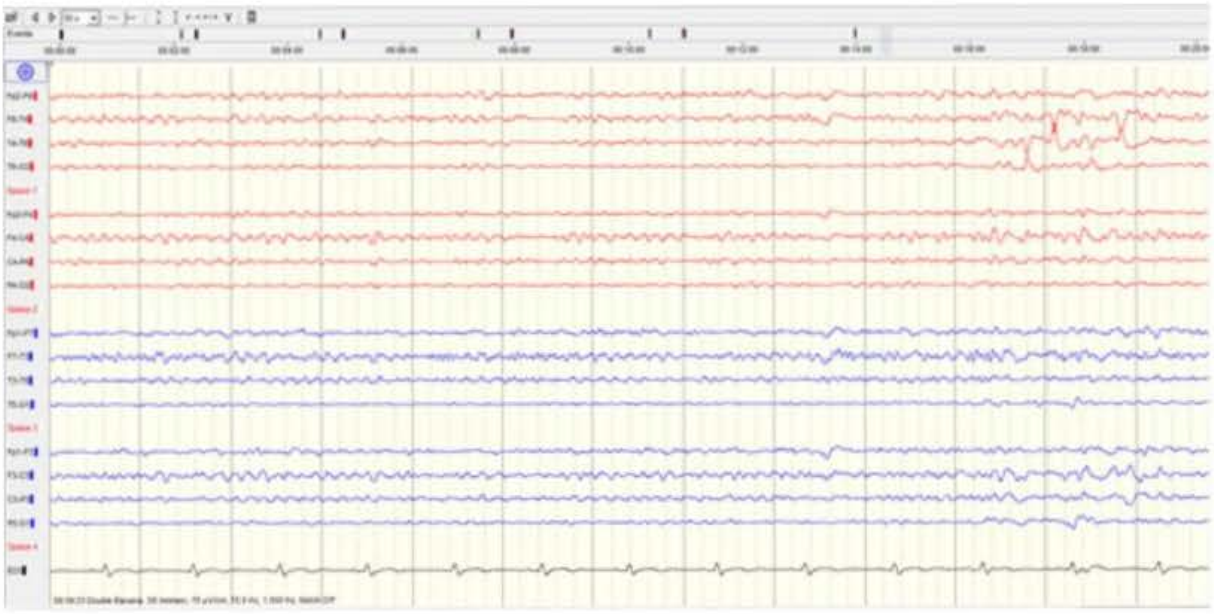

Figure 2: Mr AF's EEG showed generalised slow wave activity.

Investigation: magnetic resonance imaging (MRI)
Justification: patient has progressive neurological symptoms, and MRI is a useful modality for showing structural changes in the brain
Result & conclusion: refer to figure 3: MRI shows multiple peri-ventricular hyperintense foci in keeping with small-vessel ischaemic changes: this is consistent with the patient's cardiovascular risk factors.

Management:

Table 3 outlines the pharmacological management for this patient: Mr AF's regular medications were continued in view of his cardiovascular risk factors and prostate problems. Donepezil was prescribed: it is a cholinesterase inhibitor which can improve mental function.

Mr AF was referred for neuropsychology

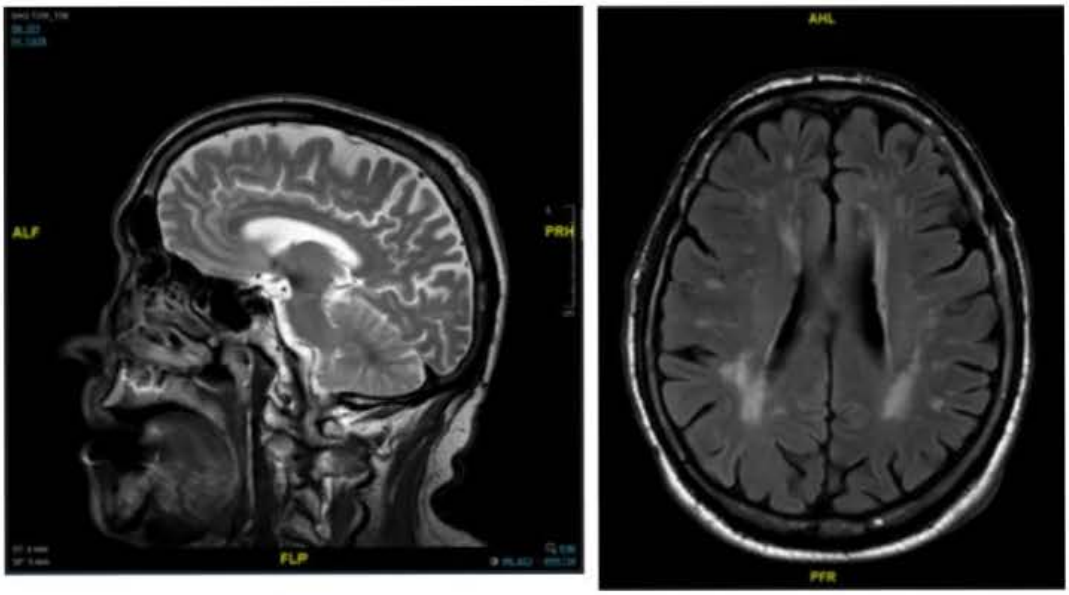

Figure 3: MRI: the axial view shows hyperintense periventricular foci. The sagittal view shows how the FTD pathological process mainly affects the frontotemporal regions.

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Aspirin	75mg PO once daily	Ischaemic heart disease
Clopidogrel	75mg PO once daily	Ischaemic heart disease
Simvastatin	40mg PO nocte	Hypercholesterolaemia
Tamsulosin	1 tab daily	Benign prostatic hyperplasia
Donepezil	5mg PO once daily	Mild cognitive impairment
Folate supplements	400µg PO once daily	Mild cognitive impairment

Table 3: Pharmacological Therapy

assessment, which confirmed mild cognitive impairment. According to his wife, Mr A.F.'s condition remained stable, however neuropsychology assessment noted decline in some functions, mostly relating to attention/recall. The patient reported that he was still capable of performing his activities of daily living independently, and his wife stated that he parks his car 'meticulously'. Notably, the patient experienced difficulty explaining himself.

Discussion: Frontotemporal Dementia

General signs and symptoms of FTD include progressive deficits in behaviour, executive function (including motor) and language. The features of the three major categories of FTD are summarised in Figure 4, and are: behavioural-variant FTD, non-fluent variant primary progressive aphasia, semantic-variant primary progressive aphasia. The likeliest subtype in this patient is behavioural-variant FTD, since it is characterised by changes in behaviour, personality and emotion control. Executive control is only lost once the dorsal lateral prefrontal cortex is affected (Seeley et al., 2007).

Inflammatory mediators such as tumour necrosis factor are involved in the pathophysiology (Bott et al., 2016).

In diagnosis, one must consider that FTD can present with symptoms that overlap with psychiatric disorders such as late-onset schizophrenia, bipolar disorder; or obsessive-compulsive disorder. Current available treatments do not cure or prevent the underlying neurodegenerative process, and mainly improve symptoms (Bott et al. 2016). Behavioural deficits can be moderately improved with the use of selective serotonin reuptake inhibitors and trazodone.

Conclusion

This case report describes the presentation, classification and treatment of frontotemporal dementia, while outlining the importance of holistic management in this patient with multiple comorbidities. This report outlines the diagnostic investigations which are necessary to distinguish frontotemporal dementia from other neurological or vascular conditions which may present in a similar manner.

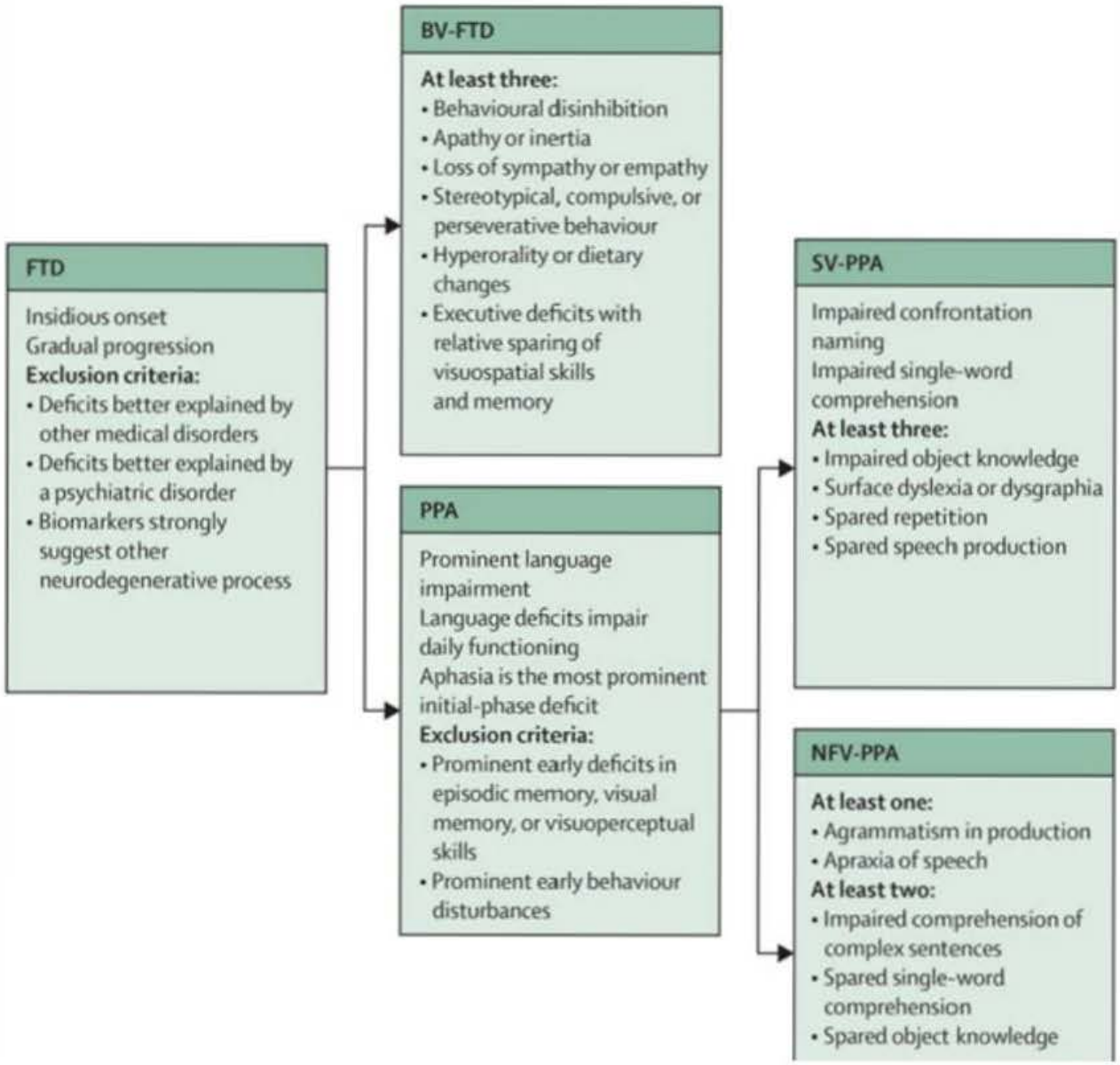

Figure 4 FTD is a clinical term which encompasses three different entities with a differing presentation.
(Source: Bang et al., 2018).

References

Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet. 2015 Oct 24;386(10004):1672-82. doi: 10.1016/S0140-6736(15)00461-4. PMID: 26595641; PMCID: PMC5970949.

Bott NT, Radke A, Stephens ML, Kramer JH. Frontotemporal dementia: diagnosis, deficits and management. Neurodegener Dis Manag. 2014;4(6):439-54. doi: 10.2217/nmt.14.34. PMID: 25531687; PMCID: PMC4824317.

Coyle-Gilchrist IT, Dick KM, Patterson K, Vázquez Rodríquez P, Wehmann E, Wilcox A, Lansdall CJ, Dawson KE, Wiggins J, Mead S, Brayne C, Rowe JB. Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. Neurology. 2016 May 3;86(18):1736-43. doi: 10.1212/WNL.0000000000002638. Epub 2016 Apr 1. PMID: 27037234; PMCID: PMC4854589.

Lanata SC, Miller BL. The behavioural variant frontotemporal dementia (bvFTD) syndrome in psychiatry. J Neurol Neurosurg Psychiatry. 2016 May;87(5):501-11. doi: 10.1136/jnnp-2015-310697. Epub 2015 Jul 27. PMID: 26216940; PMCID: PMC4755931.

Leys, D., Hénon, H., Mackowiak-Cordoliani, M. A., & Pasquier, F. (2005). Poststroke dementia. The Lancet Neurology, 4(11), 752-759.

Olney NT, Spina S, Miller BL. Frontotemporal Dementia. Neurol Clin. 2017 May;35(2):339-374. doi: 10.1016/j.ncl.2017.01.008. PMID: 28410663; PMCID: PMC5472209.

Seeley WW, Zhou J, Kim E-J. Frontotemporal Dementia: What Can the Behavioral Variant Teach Us about Human Brain Organization? The Neuroscientist. 2012;18(4):373-385.

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