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Paroxysmal nocturnal haemoglobinuria
From the first case to the current complement inhibition therapies

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Paroxysmal nocturnal haemoglobinuria (PNH) is a rare clonal disorder that affects about 1-1.5 cases per million individuals, characterised by haemolysis, peripheral blood cytopenia, bone marrow dysfunction, thrombosis, renal impairment and arterial and pulmonary hypertension. The first case of PNH was described probably in 1793 by a surgeon, Dr Charles Stewart, in the medical commentaries "Account of a singular periodical discharge of blood from the urethra". In the following decades the most eminent physicians and scientists of the time reported several cases. In 1882, Paul Strübing was the first to identify PNH as a new disease entity. Hijmans in 1911 considered the possibility that the complement system mediated the haemolysis of PNH erythrocytes and, in the same year, Italian scientists Ettore Marchiafava and Alessio Nazari scrupulously described the pathogenesis of the condition. In 1925, Enneking introduced the name "paroxysmal nocturnal haemoglobinuria", to define this pathology. Despite increased knowledge about this syndrome, therapies for PNH were still only experimental and symptomatic, with the use of antimicrobial agents, corticosteroids and blood transfusions. The natural history of PNH changed remarkably only in 2007, with the introduction of the Eculizumab complement blockade agent. Ravulizumab, a long-acting C5 complement inhibitor, approved in December 2018 by the US Food and Drug Administration (FDA), and on July 2019 by the European Commission, represents a new promising instrument for PNH treatment. A second generation of anti-complement agents is currently under investigation, representing future promising instruments for the treatment of PNH.

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Από την πρώτη περίπτωση έως τις τρέχουσες θεραπείες αναστολής συμπληρώματος

Περίληψη στο τέλος του άρθρου

Key words

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1. INTRODUCTION

Paroxysmal Nocturnal Haemoglobinuria (PNH) is a rare clonal disorder that affects about 1–1.5 cases per million individuals.[2] The condition takes its name from the characteristic severe haemolytic anaemia giving rise to episodes of haemoglobin in the urine, especially during the night.

The main features of PNH are haemolysis, peripheral blood cytopenia, bone marrow dysfunction, hypercoagulablilty, thrombosis, smooth muscle dystonia, all symptoms that can also lead to redoubtable complications such as renal failure, arterial and pulmonary hypertension and recurrent infections.[3,30]

2. HISTORY OF PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA

2.1. The origins of PNH: First cases

The first case of PNH was described probably in 1794 by Dr Charles Stewart, a Scottish surgeon practicing in Archangel, a city in the north of European Russia. In the medical commentaries "Account of a singular periodical discharge of blood from the urethra", he reported the case of a 51-year-old man, much emaciated a complaining of *"constant severe pain in the loins, passing down to the pubes and groin, passed bloody urine at times for over eight months".* He also reported that *"Each attack of haemorrhage lasted*

three days, he was cured by tincture of bark, port wine and good diet. The great wasting and constant pain, increased by movement, are unlike what is met with in paroxysmal haematuria".[4] This could be the first time that PNH has been documented in the history of the disease.

In the next decades, the most eminent physicians and scientists of the time reported several cases.

The French physician Dr Pierre François Olive Rayer in his three-volume book on diseases of the kidney titled "*Traité des maladies des reins"* (Treatise on Diseases of the Kidneys), published in 1841, gave a vague reference to the disease, describing a case of intermittent haematuria of unknown origin.[5]

The Jewish-American Cardiologist Dr William Dressler, in 1854, published a report of "Intermittent Albuminuria and Chromaturia", describing the case of a 10-year-old boy with urine containing brown amorphous pigments, the abundance of casts and no blood corpuscles.[6]

A first detailed account was described in 1866, when Sir William Gull reported a case of a young "anaemic looking" tanner with several episodes of dark urine, calling this condition "intermittent hematinuria". The patient was a leather-dye worker and in his work he was exposed to cold and humid conditions. Gull considered that this may have been a triggering cause for the syndrome. This raises the suspicion that it could have been Paroxysmal Cold Haematuria, a disease not yet distinguished from PNH at the time.

An interesting witness of the knowledge and methods used in nephrology in the XIX century came from thesis of G.H.K. Macalister for the M.D. degree at Cambridge University, in July 1909. He made a critical review on "The pathology of paroxysmal haemoglobinuria". He attributed the paternity of the definition "Paroxysmal Haemoglobinuria" to the work of Dr Secchi in 1872.[7]

The author also mentioned the experience of Dr George Johnson, who in 1873, under the name of "periodic or cyclic albuminuria", recognised a condition of intermittent haemoglobinuria, whose most commonly recognised causes were exercise, fatigue and exposure to the cold.

Macalister also reports that in 1877 Dr Stefanini and Dr Camillo Golgi performed in Pavia an autopsy on a patient who had suffered from *"emoglobinuria da freddo"* (cold haemoglobinuria) for five years. The arteries were atheromatous, the liver was quite normal, but the spleen was nearly twice the normal size. The kidneys were enlarged; the capsule fully stripped. The cortex was easily lacerated and the surface was marked with *"dark rose points"*. The medullary pyramids were hyperaemic and distinctly showed many red striae. Microscopically, they found *"una leggera nefrite diffusa e specialmente interstiziale"* (a mild diffuse and especially interstitial nephritis).

In 1880, Dr R. Lepine of Lyon published a report of a case mentioning the typical pattern of nocturnal haemoglobinuria: "It is only at night that urine was blood coloured, around 11:00 o'clock or midnight, the urine was blood-coloured and not the other specimens. The colouring was, moreover, as I have said, intense. On microscopic examination several times repeated, it demonstrated an absolute absence of red cells. The urine specimens which are not coloured are probably not entirely free of haemoglobin". Lepine contended that haemoglobinuria is in reality an unusual form of haematuria that the red cells are lost as such by the kidney, and are lysed in the very diluted urine in the renal tubules. He concluded, "In the immense majority of cases the crisis is the result of cold. But we need not believe that this is the only cause. My patient had his paroxysm at midnight when he had been in bed six hours. There are at least two distinct types of paroxysmal haemoglobinuria".[8]

In 1882, Paul Strübing identified PNH as a new disease entity, indicating that these patients could have an intravascular haemolysis with a defect of red blood cells.[9] He described a 29-year-old man who presented with fatigue, abdominal pain, and severe nocturnal paroxysms of haemoglobinuria. By provocative tests, he differentiated this affection from other forms of paroxysmal haemoglobinuria, proposing theories of pathogenesis based upon analysis of his clinical observations. He first hypothesised the nocturnal paroxysms of haemoglobinuria as a consequence of lysis of "abnormally sensitive erythrocytes" secondary to systemic acidosis from CO_2 accumulation during sleep.[10] Strübing described haemosiderinuria with these words: "a fine grained, yellowish-brown detritus and fine-grained casts of the same colour. Free in the sediment were found yellow-brown renal epithelial cells".

2.2. History of PNH: First decades of twentieth century

In 1894, Jules Bordet found that complement binds to antibody-antigen complexes regardless of the antigen or antibodies involved; for his research on the complement, he was awarded the 1919 Nobel Prize in Physiology or Medicine.[11] Fifteen years later, Dr Hijmans Van Den Bergh, in line with Bordet's discovery, considered the possibility that the complement system mediated the haemolysis of PNH erythrocytes.

He demonstrated that erythrocytes from a similar patient were lysed in normal serum as well as in the patient's

serum if the mixture was acidified with carbon dioxide.[12] He also confirmed that the haemolytic process was due to a defective red cell and related to complement dysregulation.[13]

The same year (1911), the Italian scientists Ettore Marchiafava and Alessio Nazari scrupulously described the pathogenesis of the condition. They believed that haemolysis occurred in the kidney: the scientists called the reported case "acquired haemolytic anemia, Widal-Abrami type", characterised by "massive amounts of haemosiderin in the urine".[14] In 1925, Dr Enneking introduced for the first time the name "paroxysmal nocturnal haemoglobinuria", to define this pathology.[1]

In 1928, Ettore Marchiafava reported a second case: he believed he had identified a new disease entity and he proposed that it be called "chronic haemolytic anaemia with perpetual haemosiderinuria".[15] In 1930, Micheli, Marchiafava's pupil, continued his mentor's research work. He studied Marchiafava's second patient and published his observations. Micheli termed this condition "splenomegalic haemolytic anaemia with haemoglobinuria-haemosiderinuria, Marchiafava type".[16]

In 1939, Sir Thomas Hale Ham[17] and Dr John Dingle devised the first diagnostic test for PNH based on the relationship of complement activation to the haemolysis in PNH, named the Ham test.[18]

In 1960, Metz et al[19] demonstrated that the degree of suppression of erythrocyte acetylcholinesterase activity is directly proportional to the severity of this disease.

In 1969, Aster and Enright[20] showed that PNH platelets and neutrophils are abnormally sensitive to complement-mediated lysis, providing evidence that the PNH defect arose in a primitive hematopoietic stem cell. The same year, Edward Hoffman described for the first time the decay accelerating factor (DAF) or CD 55. He found that this factor, prepared from human erythrocyte membranes, inhibited complement-mediated haemolysis. This substrate enhanced the rate at which the complement C3 convertase diminished over time.[21]

2.3. PNH: 1980s to current days

Dockter and Morrison,[22] in 1986, demonstrated with indirect immunofluorescence analysis of a monoclonal antibody specific for a surface epitope of human erythrocyte acetylcholinesterase, that the erythrocytes of PNH patients presented deficiencies in acetylcholinesterase, a GPI-anchored protein.

In 1989, Dr Charles Parker et al[23] isolated for the first time the membrane inhibitor of reactive lysis (MIRL, CD59), the encoding protein of (GPI)-anchored cell surface glycoprotein that inhibits the final step of membrane attack complex (MAC) formation.[24]

In the mid-1990s, a fundamental change was brought about in the diagnosis of PNH: flow cytometry of the peripheral blood superseded the Ham Test as the definitive clinical assay. Until 1994, patients were diagnosed using the Ham test or modified versions of the test.[25]

Brodsky et al[26] in the 2000 developed the Fluorescein-labelled proaerolysin reagent (FLAER), based on a fluorescently labelled inactive variant of the aerolysin protein that binds selectively to GPI anchors.

Despite increased knowledge of this syndrome, therapies for PNH were still only experimental and symptomatic, with the use of antimicrobial agents, corticosteroids and blood transfusions.

2.4. The present and future perspective of PNH therapy

The most significant development in PNH was the emergence and successful clinical trial of a humanised monoclonal antibody that inhibits terminal complement activation targeting haemolysis.[27] This agent is eculizumab, which, in 2007, remarkably changed the history of PNH.

Eculizumab radically modified the symptoms, biology, and natural history of PNH, strongly improving the quality of life of PNH patients.[28]

Ravulizumab, a long-acting C5 complement inhibitor approved in December 2018 by the US Food and Drug Administration (FDA), and in July 2019 by the European Commission, represents a new promising instrument for the treatment PNH. This drug is an eculizumab-like monoclonal antibody engineered to have a longer half-life. It is designed to produce the same benefits as eculizumab but with a more advantageous and effective dosing schedule.[29]

A second generation of anti-complement agents is currently under investigation, representing future promising instruments for the treatment of PNH.

3. CONCLUSIONS

The history of PNH shows many examples of the role of careful clinical observation and the application of the methods of science available at the time in unravelling this complex disorder.

As with all science, it is characterised by a series of "bricks", which solidify our understanding and which are built as more observations are made and better methods become available. The work of our eminent colleagues is an inspiration for both young and experienced researchers to unveil the mysteries of medicine.

ΠΕΡΙΛΗΨΗ

Νυκτερινή παροξυντική αιμοσφαιρινουρία: Από την πρώτη περίπτωση έως τις τρέχουσες θεραπείες αναστολής συμπληρώματος

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Η νυκτερινή παροξυντική αιμοσφαιρινουρία (ΝΠΑ) είναι μια σπάνια κλωνική διαταραχή που επηρεάζει περίπου 1–1,5 ανά εκατομμύριο ατόμων. Χαρακτηρίζεται από αιμόλυση, κυτταροπενία περιφερικού αίματος, δυσλειτουργία μυελού των οστών, θρόμβωση, νεφρική ανεπάρκεια και αρτηριακή και πνευμονική υπέρταση. Η πρώτη περίπτωση ΝΠΑ περιγράφηκε πιθανότατα το 1793 από έναν χειρουργό, τον Dr Charles Stewart, στις ιατρικές σημειώσεις «Περιγραφή μιας ιδιαίτερης περιοδικής έκκρισης αίματος από την ουρήθρα». Τις επόμενες δεκαετίες αναφέρθηκαν αρκετές περιπτώσεις, από τους πιο διακεκριμένους ιατρούς και επιστήμονες της εποχής. Το 1882 ο Paul Strübing ήταν ο πρώτος που αναγνώρισε την ΝΠΑ ως μία νέα ασθένεια. Ο Hijmans το 1911 εξέτασε την πιθανότητα της διαμεσολάβησης του συστήματος συμπληρώματος στην αιμόλυση των ερυθροκυττάρων της ΝΠΑ και, το ίδιο έτος, οι Ιταλοί επιστήμονες Ettore Marchiafava και Alessio Nazari περιέγραψαν σχολαστικά την παθογένεση της ασθένειας. Το 1925 ο Enneking εισήγαγε για πρώτη φορά τον όρο «νυκτερινή παροξυντική αιμοσφαιρινουρία» για να περιγράψει την παθολογία. Παρά την αυξημένη γνώση περί αυτού του συνδρόμου, οι θεραπείες για την ΝΠΑ ήταν ακόμα μόνο πειραματικές και συμπτωματικές, με τη χρήση αντιμικροβιακών παραγόντων, κορτικοστεροειδών και μεταγγίσεων αίματος. Η φυσική ιστορία της ΝΠΑ άλλαξε αξιοσημείωτα μόνο το 2007, με την εισαγωγή του παράγοντα αποκλεισμού συμπληρώματος eculizumab. Το ravulizumab, ένας αναστολέας συμπληρώματος C5 μακράς δράσης που εγκρίθηκε το Δεκέμβριο του 2018 από τον Αμερικανικό Οργανισμό Τροφίμων και Φαρμάκων (FDA) και τον Ιούλιο του 2019 από την Ευρωπαϊκή Επιτροπή, αποτελεί ένα νέο πολλά υποσχόμενο μέσο για τη θεραπεία της ΝΠΑ. Η δεύτερη γενιά αντι-συμπληρωματικών παραγόντων βρίσκεται υπό έρευνα, αντιπροσωπεύοντας μελλοντικά ελπιδοφόρα μέσα για τη θεραπεία της ΝΠΑ.

Λέξεις ευρετηρίου: Αναστολή συμπληρώματος, Εκουλιζουμάμπη, Νόσος Marchiafava-Micheli, Νυκτερινή παροξυντική αιμοσφαιρινουρία, Ραβουλιζουμάμπη

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