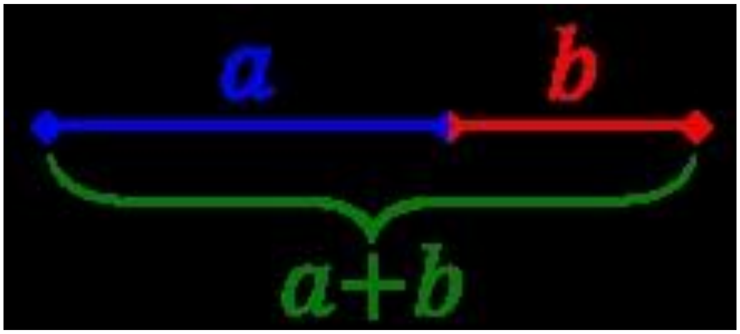
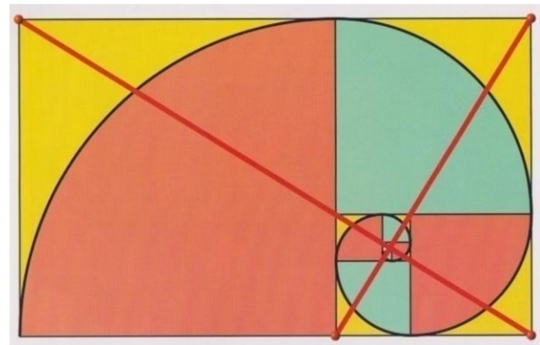
NEPHROTIC SYNDROME

Veronica Lake, c.1930, Paramount Pictures.

"A straight line is said to have been cut in extreme and mean ratio when, as the whole line is to the greater segment, so is the greater segment to the lesser segment".

Euclid, 3rd/4th Century B.C





Left: The Golden Ratio of a line segment; (a + b)/a = a/b. Right: A Golden Rectangle, showing the point of infinite regress - the "Eye of God".

The mathematician Paul Dirac once pondered whether God was a mathematician. Mathematical laws and special numbers seem to underlie the very fabric of nature and the Universe. Some even seem to inspire a deep primal sense of aesthetic value in the human mind, though why this should be is completely mysterious. The ancient Pythagoreans attached mystical powers to certain special numbers, which seemed to recur throughout nature, spawning a cult of priestly "numerologists" in subsequent centuries. There are many enigmatic numbers that seem to be ubiquitous within nature and physics, including pi, e, and i, but the most enigmatic of all is possibly phi, (Φ), (named for the Greek master sculptor Phidias). This number is a seemingly innocuous ratio, but it possesses deeply mysterious properties, appearing with amazing frequency in mathematics, physics and nature. In the anthropomorphic sense we see it in ancient classical architecture, as well as the art of the High Renaissance.

In the Thirteenth century, Fibonacci described a famous series of numbers, 0, 1, 1, 2, 3, 5, 8, 13, 21, 34.....where each integer is the sum of the preceding two. The further the series progresses, the closer the ratio of one of the numbers to its predecessor gets to Φ. The science writer, Philip Ball has pointed out that, "It is widely claimed that the phyllotaxis classification of leaves, petals, or floret patterns in any plant species always correspond to pairs in this series. A corollary of this is that the number of petals on most flowers should be a Fibonacci number, since petals, like florets, are modified leaves. And indeed buttercups have 5 petals; marigolds have 13, asters 21". The heads of sunflowers contain interlocking clockwise and anticlockwise spirals of seeds. The number of spirals (as well as the number of petals) is very often a Fibonacci number. But why should nature follow a seemingly abstract mathematical series?

The exact value of Φ cannot be defined, as it is an irrational number, with an infinite series of numbers following its decimal point. It can be written as 2/(√5 -1). Euclid however, defined it in the Third Century B.C in terms a famous mathematical ratio; known as the "Golden Ratio". It is a line divided into two, such that the ratio, of the long *segment to short segment equals the ratio of the total length to the long segment. Its value comes to 1.61803.....*

If a Golden Rectangle is constructed, i.e. the sides are in the proportions of the Golden Ratio, then a multitude of fascinating properties emerge. It is possible to divide a golden rectangle into a square and another smaller golden rectangle. The smaller golden rectangle can then be further subdivided into a square and a still smaller golden rectangle. This process can be continued indefinitely into infinitely smaller golden rectangles. Now if we draw a diagonal across the original rectangle and a second diagonal in the next smaller rectangle crossing the first diagonal at right angles, the intersection point marks the point where all the successively smaller rectangles converge toward. This point of infinite regress has been named the "Eye of God". Stunningly the lengths of the crossed diagonals are all in golden ratio to each other. The golden rectangle is the ***only*** *rectangle from which a square can be cut, so that the remaining rectangle will be similar to the original rectangle. Now the truly stunning property of all this is that if we connect the opposite vertices of the rectangles in a continuous line, we approximate a logarithmic curve that spirals into the eye of God, like a light wave into an infinitely small singularity! The logarithmic spiral abounds in nature, anywhere where there is a need to fill space regularly and economically where strength is required with the minimum of materials. While expanding the size increases, but never the shape. In nature we see this in nautilus shells, animal horns, and the human cochlea.*

The ancient Greeks of classical times considered the golden ratio to be the most perfect proportion in nature. It had a primal aesthetic to the human eye, and it has been said that important architectural aspects of many temples where based on this ratio, including - allegedly - the proportions of the elevation of the Parthenon. Over two thousand years ago Euclid recognised the crucial role of the ratio in the construction of the geometric form of the pentagram, to which he attributed magical properties. Although somewhat controversial, some expert historians of music have claimed that Johann Sebastian Bach built Fibonacci sequences into some of his scores. Many works of Renaissance art, particularly some of Leonardo da Vinci's works show the logarithmic spiral hidden within them, most notably in his "Study for the Head of Leda". Leonardo used this shape many times especially in his studies of clouds, and in sketches of the swirling waters for the "Deluge". The classical Greek architects, obsessed with the idea of perfect proportions even extended the ideal to the human body - the perfectly proportioned Adonis, was said to have a proportion of a ratio of the height to the navel to the total height equal to Φ. The ideal female proportions with the most pleasing overall appeal to the eye, has been highlighted as those of the vital statistics of the golden age of Hollywood film star of the 1930s, the most sensuous Veronica Lake who had the power to make any man swoon. At the peak of her career in the early 1930s, the ratio of her chest measurement of 34 inches to that of her waist of 21 inches was a perfect Fibonacci sequence, with a ratio very close to Φ!

When we strive to understand nature, we do so in particular by means of an especially useful meme, the human mental construct we call mathematics. Formulas and ratios help us to understand her deepest secrets. When it comes to the assessment of patients with possible nephrotic syndrome, although not quite as elegant as Φ, we have at our disposal our own "Golden Ratio", that of the urinary protein to creatinine.

NEPHROTIC SYNDROME

Introduction

Nephrotic syndrome is a clinical disorder characterized by:

- **Oedema**
- **Proteinuria (massive, often > 3.5 grams per 24 hours)**
- **Hypoalbuminaemia (<30 g/L)**
- **Hypercholesterolaemia.**

Prognosis is variable depending on the underlying cause of the syndrome.

Nephrotic syndrome versus nephritic syndrome

Note that **nephrotic syndrome** is a distinct syndrome to the **nephritic syndrome.**

Nephritic syndrome consists of:

- *Haematuria*
- *Oliguria*
- *Uraemia (azotemia)*
- *Hypertension*

Epidemiology

Nephrotic syndrome can affect all age groups and both sexes.

In children, it is most common between ages 2 and 6.

Pathophysiology

Causes

Nephrotic syndrome has many causes which may be due either primary kidney disease or secondary to systemic diseases.

In all cases, **glomerular injury** is a constant feature. Kidney diseases that affect only the tubules and interstitium, such as interstitial nephritis, do not cause nephrotic syndrome.

Causes include:

1. Primary renal causes:

- Minimal-change nephropathy:

    - ♥ This is the commonest cause in children.

      Minimal change glomerulonephritis accounts for 80-85% of nephrotic syndrome in childhood. [1]

    - ♥ It is called “minimal change” because the kidney filters appear normal under a microscope. The cause is thought to be changes in certain cells of the immune system. The function of the kidneys is normal and the outlook for recovery is usually excellent.

- Focal glomerulosclerosis

- Membranous glomerulonephritis

    - ♥ This is the most common cause in adults.

- Hereditary nephropathies

2. Secondary causes:

- Diabetes mellitus:

    - ♥ This is the commonest secondary cause.

- Amyloidosis

- Paraproteinaemias (predominantly multiple myeloma).

- Systemic lupus erythematosus

- Some viral infections:

    - ♥ Hepatitis B

    - ♥ Hepatitis C

    - ♥ HIV

- Pre-eclampsia

- Drug toxicity:

    - ♥ NSAIDs have been implicated.

Complications

These may include:

1. Fluid balance disturbances:

    - Hypovolaemia (from excessive intravascular fluid depletion)

    - Congestive cardiac failure and pulmonary oedema may also be seen (from excessive extravascular fluid retention).

2. Renal impairment:

    This can be:

    - Acute:

        ♥ Primarily due to renal hypoperfusion

    - Chronic:

        ♥ Due to glomerular destruction.

3. Thromboembolic disease:

    - Thrombosis may occur in nephrotic patients due to a combination of hypovolaemia, high platelet counts and loss of antithrombin III [1]

4. Infection:

    - Impairment of the immune system may occur in patients with the nephrotic syndrome possibly due to the urinary loss of immunoglobulins and complement proteins.

5. Hyperlipidaemia and accelerated atherosclerosis:

    - Due to decreased LDLs and elevated cholesterol, possibly from loss of plasma factors regulating lipoprotein synthesis. [2]

6. Hypocalcaemia:

    - Usually secondary to a low serum albumin level.

Clinical features

Clinical features of the nephrotic syndrome include:

1. General constitutional systems

- Lethargy/ malaise
- Anorexia

2. Weight gain (unintentional) from fluid retention
3. Oedema:

   This is the hallmark clinical feature of the nephrotic syndrome and is due to hypoalbuminaemia

   - Periorbital oedema is a common early symptom
   - This may progress to dependent then to becomes generalized oedema (limbs)
   - Ascites and pleural effusions are very late signs

4. Excessive proteinuria can make the urine appear frothy or foamy
5. Orthostatic hypotension:

   - Intravascular fluid depletion due to lowered intravascular oncotic pressures

Differential diagnoses of generalized oedema:

These will include:

1. Protein losing enteropathies (with low albumin)
2. Chronic liver failure (with low albumin)
3. Congestive cardiac failure
4. Pre-eclampsia and eclampsia.

Investigations

Blood tests:

1. FBE:

   - Anaemia may suggest chronic kidney disease

2. U&Es/ Creatinine/ eGFR

   - Renal impairment

3. Glucose

- Check for diabetes

4. Blood lipids

5. Calcium and phosphate levels

6. LFTs:

- Look for total protein, albumin and globulin levels.

Other more specialized tests may be done according to the degree of clinical suspicion for any given condition

Urine:

1. FWT:

- Urinalysis shows heavy proteinuria, (3+ or 4+ is usual)

2. 24-hour urine collection:

- Normally a person loses less than 150mg of protein in the urine in a 24-hour period.

- A person with nephrotic syndrome can lose more than 3.5 grams or more of protein in the urine during a 24-hour period (i.e. about 25 times the normal amount).

3. Spot urine protein/creatinine ratio, (>2):

- Alternatively a single spot urine collection is much easier to obtain

  When the ratio of urinary protein to urinary creatinine is greater than 2 grams protein per one gram of creatinine, this corresponds to about 3 grams of urine protein per day or more.

3. Microscopy:

- Microscopic haematuria is present in 15 - 20% of patients with minimal change nephrotic syndrome.

- For **glomerular casts**, indicating glomerular disease.

Ultrasound

To assess the kidneys. Small kidneys suggest chronic disease.

CT Scan

CT without contrast is another option for visualizing the kidneys.

MRI

MRI is the best imaging option to visualize the kidneys, but is not generally necessary for cases of nephrotic syndrome.

Biopsy

Kidney biopsy will often be done to establish a definitive diagnosis, especially in cases of intrinsic renal disease.

Management

Management is directed toward the underlying cause, as well as to any secondary complications.

Management is tailored to the individual by a renal physician.

In general terms:

1. Diet:

    - Salt restriction.

2. Strict fluid balance observation

    - Fluid restriction per se it not necessary, unless there are clinical complications from fluid overload.

3. Albumin: [1]

    Give in consultation with a Renal physician.

    Intravenous albumin is generally indicated for:

    - Anuria

    - Hypotension, with poor skin perfusion with skin mottling or poor capillary return.

    Give 20% albumin 5 ml/kg (1 gram/kg) over 4 hours IV.

    Beware of the possibility of pulmonary oedema.

    Frusemide should only be given if the peripheral perfusion markedly improves following the albumin or there are signs of pulmonary oedema or hypertension.

4. ACE inhibitors or angiotensin blockers:

    - These can reduce the amount of proteinuria.

5. Penicillin:

    - Prophylactic oral penicillin while acutely oedematous.

6. Low dose aspirin:

    - For thromboembolic prophylaxis

7. Statins to help with cholesterol control

8. Diuretics:

    - Frusemide/ spironolactone, are often used to control excessive peripheral oedema.

9. Corticosteroids:

    - There is variable response to these, depending on the underlying cause.

10. Immunosuppressives:

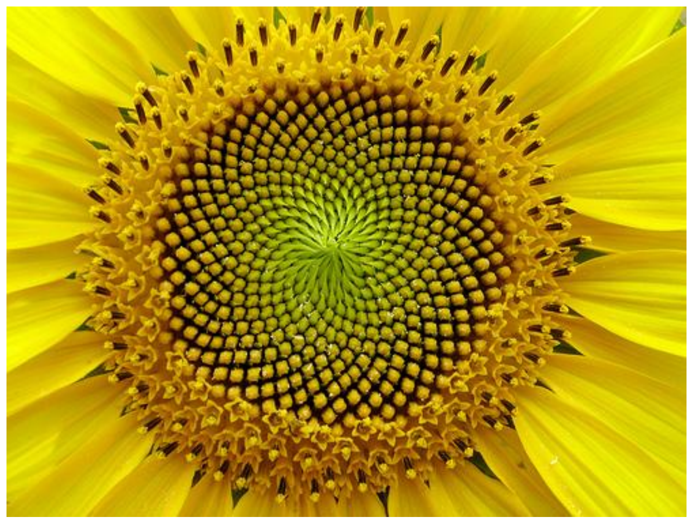
    - These are sometimes used in severe cases, and again the decision to use these will also be influenced by the underlying cause.

    - Cyclophosphamide and cyclosporine are generally used.

Disposition

In general first presentations are usually admitted to hospital under the Renal Unit.

Cases of relapses in patients with an established diagnosis may not require admission, but should always be discussed with the Renal Physician.



Left: Study for the Head of Leda, chalk and ink on paper, Leonardo da Vinci, High Renaissance Period, c. 1506, The Royal Collection, Windsor Castle.

An intricately crafted logarithmic spiral is seen in the woman's tressed hair.

Right Above, A section through the beautiful chambered Nautilus, Right Below: The equally beautiful logarithmic counter-spirals of the seeds of a sunflower.

References

1. RCH Clinical Guidelines.

2. Talley NJ, O’Conner S, Clinical Examination, 3rd Ed 1996.

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