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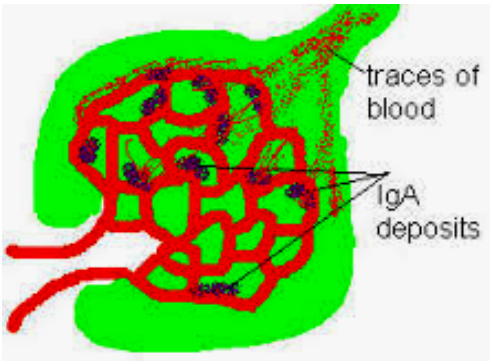
Berger's Disease (IgA Nephropathy)

Introduction



Since its first description by Berger and Hinglais in 1968, IgA nephropathy (IgAN) has remained the most common form of idiopathic glomerulonephritis leading to chronic kidney disease (CKD) in developed countries.

IgAN is an autoimmune renal disease arising from consequences of increased circulating levels of IgA1 with galactose-deficient hinge-region O-glycans. For this to cause kidney injury, several further processes are required, including synthesis of circulating antibodies directed against the aberrantly glycosylated O-linked hinge-region glycans to form immune complexes, accumulation of the complexes in the mesangium, and activation of mesangial cells. Genetic factors apparently influence the expression of these processes.

Symptoms

IgA nephropathy usually doesn't cause symptoms in the early stages. The disease can go unnoticed for decades and is sometimes first suspected when routine tests reveal protein and red blood cells in the urine that can't be seen without a microscope (microscopic hematuria).

Signs and symptoms of IgA nephropathy when kidney function is impaired include:

- Cola- or tea-colored urine (caused by red blood cells in the urine)
- Repeated episodes of cola- or tea-colored urine, sometimes even visible blood in the urine, usually during or after an upper respiratory or other type of infection
- Pain in the side(s) of the back below the ribs (flank)
- Foam in the toilet water from protein in the urine
- Swelling (edema) in the hands and feet
- High blood pressure

Causes

Immunoglobulin A (IgA) is an antibody that plays a key role in the immune system by attacking invading pathogens and fighting infections. But in IgA nephropathy, this antibody collects in the glomeruli, causing glomerulonephritis and gradually affecting their filtering ability.

Researchers don't know exactly what causes IgA deposits in the kidneys, but these conditions or factors may be associated with the development of IgA nephropathy:

- **Genes**, because IgA nephropathy is more common in some families and in certain ethnic groups
- **Liver diseases**, including cirrhosis, and chronic hepatitis B and C infections
- **Celiac disease**, a digestive condition triggered by eating gluten in most grains
- **Dermatitis herpetiformis**, an itchy, blistering skin disease that stems from gluten intolerance
- **Infections**, including HIV infection and some bacterial infections

Complications

- **High blood pressure**. Damage to the kidneys from IgA deposits can raise the blood pressure, and high blood pressure can cause further damage to the kidneys.
- **High cholesterol**. High levels of cholesterol increase the risk of heart attack.
- **Acute kidney failure** due to rapidly progressive glomerulonephritis.

- **Chronic kidney failure**. IgA nephropathy can cause the kidneys to gradually stop functioning. In such cases, permanent dialysis or a kidney transplant is needed.
- **Nephrotic syndrome**. This is a group of problems that can be caused by damage to the glomeruli, including high urine protein levels, low blood protein levels, high cholesterol and lipids, and edema of the eyelids, feet and abdomen.

Tests and diagnosis

- **Urine testing** by dipstick will probably show light-to-moderate albumin and blood.
- **Urine microscopy** is required for red blood cells, leukocytes and casts.
- Measurement of 24 hours of protein excretion should be undertaken. A semi-quantitative estimate from a spot urine and extrapolation based on creatinine content is less satisfactory. If the patient is over 50, protein electrophoresis should be undertaken to exclude myeloma.
- Assess **kidney function** with U&Es (urea and Electrolytes), creatinine and a 24-hour creatinine clearance test.
- **Plasma levels of IgA** are raised in about half of cases. Raised levels of plasma IgA also occurs in other conditions and the predictive value of this test is poor.
- **Serum undergalactosylated IgA** is being investigated as a diagnostic test and may lead to further elucidation of the pathogenesis of the condition.
- **The current gold-standard diagnostic test** of IgAN is by ***renal biopsy***.
- Light microscopy, electron microscopy and immunofluoresence are required.

Management

No specific therapy is available for IgAN. Lowering blood pressure and renin-angiotensin system inhibition remains the cornerstone of management. The use of steroids has been controversial but studies have shown a benefit of steroids in reducing proteinuria and reducing the risk of progression to CKD (chronic kidney disease) and ESKD (end stage kidney disease)

Patients with haematuria but no albuminuria need monitoring by urinalysis, kidney function and checking blood pressure.

Angiotensin-convertingenzyme (ACE) inhibitors/angiotensin-II-receptor antagonists (AIIRAs).

❖ Hypertension needs early and aggressive treatment. ACE inhibitors are the drugs of choice with AIIRAs in reserve. They protect kidney function and may even be beneficial with normal blood pressure.

❖ However, more evidence is needed to understand the magnitude of benefit and the possible risks of anti-hypertensive or more specifically of ACE inhibitor/AIIRA therapy alone or in combination, and which specific types of patients with the IgAN might have the greatest potential for benefit.

❖ Combination therapy using ACE inhibitors and an AIIRA may provide more benefits to IgAN patients for reducing daily proteinuria.

Steroids. Steroid therapy is associated with a decrease of proteinuria and with a statistically significant reduction of the risk of ESKD.

► Corticosteroids should be given for six months to patients with preserved kidney function, nephrotic syndrome and few histological changes on light microscopy. A typical regime is 1 g of intravenous methylprednisolone for three consecutive days at the beginning of months one, three and five, with low-dose oral steroids every other day for six months. There may be benefit in extending beyond the six-month period.

► Introduction of corticosteroids at an early stage in patients with proliferative IgAN slows the development of pathological histological changes and reduces proteinuria.

In patients with modest proteinuria, (1.5-3.5 g/day) corticosteroids slow deterioration of kidney function.

► Two-year combination therapy using prednisolone, azathioprine, heparin-warfarin, and dipyridamole early in the disease process ameliorates the activity of the acute phase of nephritis and improves the long-term outcome of severe childhood IgAN.

- One study found that a combination of steroids with an ACE inhibitor was better than an ACE inhibitor alone in reducing the progression of kidney disease.
- A combination of methylprednisolone and cyclophosphamide has been found to improve kidney function and reduce haematuria and proteinuria in children with IgAN.
- One study has reported benefits with lisinopril in children with mild IgAN.
  ESKD requires dialysis or transplantation. Recurrence of IgAN after kidney transplantation is an important cause of graft failure. Tonsillectomy improves not only clinical findings but also ameliorates histological damage caused by recurrent IgAN after kidney transplantation.

Prognosis

The degree of proteinuria is one of the strongest predictors of outcome. The risk for CKD increases with higher levels of proteinuria.
Other features of poor prognosis are sustained hypertension, impaired kidney function, and persistent haematuria. Histological findings of interstitial fibrosis, tubular atrophy and glomerular scarring give a worse outcome. As with other glomerular diseases, the risk of progression is more closely correlated with tubulointerstitial pathology than with glomerular disease.

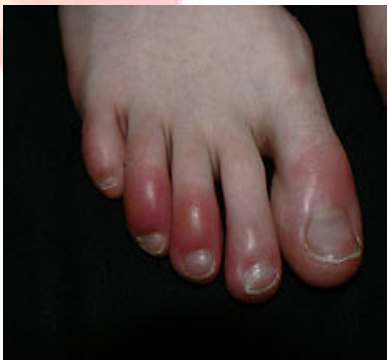
Prevention

The value of a screening programme to detect microscopic haematuria in school children in Korea has been demonstrated but its benefits in the UK with a much lower prevalence may be doubted.

References: *1) www.mayoclinic.org/diseases-conditions/iga-nephropathy/basics/treatment/con-20034366*
2) www.patient.co.uk/doctor/iga-nephropathy-bergers-disease-pro

Terminology

Chilblain



Chilblains (sometimes called pernio) are small, itchy, painful, red swellings on the skin. Chilblains are caused by an abnormal skin reaction to cold. They tend to occur on 'extremities' that more easily become cold. That is, the toes, fingers, nose and earlobes. However, The tiny blood vessels under the skin constrict when the skin becomes cold. The blood supply to areas of skin may then become very slow. As the skin ***re-warms*** there is some leakage of fluid from the blood vessels into the tissues. In some way this causes areas of inflammation and swelling leading to chilblains. Some people get chilblains if they warm up cold skin too quickly. For example, with a hot water bottle.Chilblains can be reduced by keeping the feet and hands warm in cold weather, and avoiding extreme temperature changes.

Source: *www.patient.co.uk/leaflets/erythema_pernio.htm*

Complementary Medicine
Cranberry

Species (Family):

Vaccinium macrocarpon Aiton (Ericaceae)
Vaccinium oxycoccus L.

Part(s) Used: Fruit (whole berries)

Constituents: Acids Citric, malic, quinic and benzoic acids Carbohydrates Fructose and oligosaccharides.Phenolics Anthocyanins and proanthocyanidins.

Other constituents Trace glycoside has been isolated from V.oxycoccus.
Cranberries are also a good source of fibre.Cranberry juice cocktail contains more carbohydrate than do products (i.e. soft or hard gelatin capsules) based on cranberry powder (prepared from rapidly dried fruits), whereas the latter contain more fibre.Alkaloids (N-methylazatricyclo type) have been isolated from the leaves.

Food Use: Cranberries are commonly used in foods.

Herbal Use: Cranberry juice and crushed cranberries have a long history of use in the treatment and prevention of urinary tract infections. Traditionally, cranberries have also been used for blood disorders, stomach ailments, liver problems, vomiting, loss of appetite, scurvy and in the preparation of wound dressings.

Dosage: The doses used in clinical trials of cranberry for prevention of urinary tract infections have been variable. One study used 300 mL cranberry juice cocktail (containing 30% cranberry concentrate) daily for six months.

Pharmacological Actions

Documented activity for cranberry is mainly of its use in the prevention and treatment of urinary tract infections. Initially it was thought that the antibacterial effect of cranberry juice was due to its ability to acidify urine and, therefore, to inhibit bacterial growth. However, recent work has focused on the effects of cranberry in inhibiting bacterial adherence and on determining anti-adhesion agents in cranberry juice.

Bacterial adherence to mucosal surfaces is considered to be an important step in the development of urinary tract infections; it is facilitated by fimbriae (proteinaceous fibres on the bacterial cell wall) which produce adhesins that attach to specific receptors on uroepithelial cells.

Side-effects, Toxicity

It has been claimed that ingesting large amounts of cranberry juice may result in the formation of uric acid or oxalate stones secondary to constantly acidic urine and because of the high oxalate content of cranberry juice. However, it has also been stated that the role of cranberry juice as a urinary acidifier has not been well established. The use of cranberry juice in preventing the formation of stones which develop in alkaline urine, such as those comprising magnesium ammonium phosphate and calcium carbonate, has been described.

Drug interactions

There are several reports of an interaction between cranberry juice and warfarin (increase risk of bleeding).

The mechanism for the interaction between cranberry constituents and warfarin is not known. The suggestion that it may involve inhibition of the cytochrome P450 enzyme CYP2C9 (by which warfarin is predominantly metabolized), requires investigation.

Patients taking warfarin should be advised to avoid taking cranberry juice and other cranberry products unless the health benefits are considered to outweigh the risks.

Pregnancy and lactation

There are no known problems with the use of cranberry during pregnancy. Doses of cranberry greatly exceeding the amounts used in foods should not be taken during pregnancy and lactation.

Source: Barnes, J., Anderson, L. A., and Phillipson, J.D.2007. *Herbal Medicines,* 3rd ed. London: Pharmaceutical Press.

Test Your Knowledge

1. During ovulation, peak plasma concentration(s) of which of the following hormone(s) will be reached?
   I. luteinizing hormone (LH)
   II. follicle-stimulating hormone (FSH)
   III. Progesterone
   (A) I only
   (B) III only
   (C) I and II only
   (D) II and III only
   (E) I, II, and III

2. Parenteral containers of potassium chloride concentrate must be packaged
   (A) as single-dose units only
   (B) in vials not greater than 20 mL capacity
   (C) in vials with a capacity of 10 mL or less
   (D) with a black flip-off button
   (E) with a red flip-off button

3. Two hours after receiving the last dose of heparin (9000 units IV), a male patient begins bleeding from the gums after brushing his teeth.
   What is the most appropriate clinical action
   (A) inject 10 mg of phytonadione (Aqua MEPHYTON) IV
   (B) inject 10 mg of phytonadione (Aqua MEPHYTON) 1M
   (C) inject 30 mg of protamine sulfate 1M
   (D) swab a small amount of epinephrine 1:100 onto the gum tissue to produce local vasoconstriction
   (E) discontinue heparin administration and wait for the anticoagulant effect to subside

Ask the Expert

What dietary factors can play a favourable role in the management of patients with asthma?

Several studies have examined the possible role of nutrients and food groups on asthma patients. Evidence suggests that the suboptimum intake of antioxidants could increase the risk of asthma. Recent

publications support the favourable effect of the adherence to the Mediterranean diet and to increased fruit intake, wholegrain cereals and flavonoid-rich foods in asthma prevention and treatment, while adherence to the Mediterranean diet during pregnancy lowers the risk of the development of asthma and atopy in the neonate and during its childhood. Especially in children, a high fruit intake and adherence to the Mediterranean diet has been associated with the improvement of the symptoms of asthma and rhinitis, while it has been shown to be an independent protective factor for wheezing, irrespective of obesity and physical activity. Moreover, increased magnesium, selenium, zinc and copper intake and the limitation in sodium intake have also been shown to have a favourable effect. In epidemiological studies, in populations with increased omega-3 fatty acids intake, a lower prevalence of asthma has been reported. The possible mechanism of the protective effect of omega-3 fatty acids probably rests with their anti-inflammatory properties, but this positive effect has not been confirmed in clinical studies. Apart from the role of nutrients, the achievement and maintenance of a healthy body weight and an overall nutritional balance have been shown to improve respiratory function in obese patients.

***Source**:* Katsilambros, N, Dimosthenopoulos,C., Kontogianni, M., Manglara, E., and Poulia, K-A. 2010. *Clinical Nutrition in Practice,* 1st ed. Oxford: Wiley-Blackwell.

Real Enquiries

At the "Drug Information Center", we respond to enquiries from the professional health team as well as from others. Here's one of the enquiries received at the center!

Enquiry received from: Ph. Doaa Samy, Pediatric hospital, .Assiut,Uni.
Enquiry: Can I use the residual part from metronidazole vial?

***Summary of* Answer:**

Do not remove unit from overwrap until ready for use. The overwrap is a moisture barrier. The inner bag maintains the sterility of the product. After removing overwrap, check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.
This is a single dose container, discard any unused solution

FDA News

FDA approves Raplixa to help control bleeding during surgery

On April 30-2015, The U.S. Food and Drug Administration approved Raplixa (fibrin sealant [human]), the first spray-dried fibrin sealant approved by the agency. It is used to help control bleeding during surgery.

Raplixa is a biological product approved for use in adults to help control bleeding from small blood vessels when standard surgical techniques, such as suture, ligature or cautery, are ineffective or impractical. When applied to a bleeding site.

Raplixa is dissolved in the blood and a reaction starts between the fibrinogen and thrombin proteins. This result in the formation of blood clots to help stop the bleeding. Raplixa contains fibrinogen and thrombin, two proteins found in human plasma, the liquid portion of blood. The two protein components are individually purified using a manufacturing process that includes virus inactivation and removal steps to help reduce the risk for the transmission of blood-borne viruses. The fibrin sealant components are then spray-dried, blended and packaged in a vial. Raplixa can be applied directly from the original product vial or by spraying with a delivery device onto a bleeding site. It is approved for use in conjunction with an absorbable gelatin sponge.

This approval provides surgeons an additional option to help control bleeding during surgery when needed, The spray-drying process used to manufacture Raplixa produces dried powders that can be combined into a single vial. This eliminates the need to combine the fibrinogen and thrombin before use and allows the product to be stored at room temperature.

In support of approval, the FDA reviewed data from a clinical study involving 719 participants, over 11 months, undergoing different types of surgical procedures. The study demonstrated Raplixa's effectiveness by comparing the reduction in the time needed for bleeding to stop when using this fibrin sealant and the time needed for bleeding to stop when using an absorbable sponge alone.

The most commonly reported adverse reactions were surgical pain, nausea, constipation, fever and decreased blood pressure.
Raplixa is manufactured by ProFibrix BV, a wholly owned subsidiary of The Medicines Company, based in Parsippany, New Jersey.

Source: *www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm434288.htm*

Answers:

1. (C) During the menstrual cycle, levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) vary widely. At the time of ovulation, the concentration of each of these hormones reaches a peak, coinciding with the release of the ovum and the complete development of a mature endometrial wall.

2. (D) Potassium chloride concentrate solutions are potentially very dangerous if infused undiluted. Because of numerous fatalities in hospitals, the FDA specifies that it is the only product that must be packaged in vials with black flip-off buttons. There is no color code for other parenteral solutions that are packaged in vials.

3. (E) Because of heparin's brief duration of action,mild hemorrhaging is usually treated by simply withdrawing the drug. In the presence of severe hemorrhage, the use of a specific heparin antagonist (e.g., protamine sulfate) is imperative. Usually, 1 mg of protamine sulfate IV will neutralize 100 units of heparin. However, after the IV administration of heparin, the quantity of protamine required decreases rapidly with time. Only 0.5 mg of protamine is required to neutralize 100 units of heparin 30 minutes after IV administration of heparin.