Calls to improve 'sticky blood' diagnosis

Earlier diagnosis and treatment of a common blood condition could prevent heart attack, stroke, DVT and miscarriage – delivering huge savings to the NHS. Yet patients with Hughes Syndrome continue to experience long delays in obtaining a test and often have to endure multiple miscarriages before referral is considered. **LOUISE FRAMPTON** reports.

Photo by Catherline Ashmore.

Professor Graham Hughes.

Head of the London Lupus Centre at London Bridge Hospital, Professor Graham Hughes is calling for improvements to be made in the recognition, diagnosis and treatment of antiphopholipid syndrome (APS). Despite being first described in 1983, clinicians' awareness of APS and the spectrum of symptoms associated with this autoimmune disease remains "patchy", often resulting in long delays between initial presentation and referral for tests. Tragically, many young patients are only diagnosed after experiencing stroke, heart attack or multiple miscarriage – which, in many cases, could have been easily prevented with simple, low-cost aspirin.

Prof. Hughes explained that the condition was first discovered in Lupus patients who exhibited a tendency to have "sticky blood".

However, it is also prevalent outside of this patient group. Now known as "Hughes Syndrome", it is responsible for 1 in 5 young strokes[1] in the under 45s, 21% of heart attacks under the age of 45[2] and 1 in 5 cases of deep vein thrombosis (DVT).[3] In pregnancy, it is also now recognised as one of the leading causes of recurrent miscarriage.[4]

"The immune system in these patients is over-productive and there are a number of theories as to how this may lead to an increased tendency towards venous and arterial blood clots. The antibodies may affect the phospholipids, leading to increased platelet 'stickiness'; the inside lining of the blood vessels (endothelium) may be altered; or the antibodies may affect the actual clotting proteins of the blood," Prof. Hughes explained.

The two organs of the body that are most sensitive are the brain and the placenta. In young women there may be inadequate blood supply to the foetus, which can result in spontaneous abortion – with some women having as many as 12 or 14 miscarriages.

"Although Hughes Syndrome is now considered to be common, we know from patient experience that there are often delays in diagnosis, with high costs to the NHS and the patient. A recent study found that, on average, it takes a patient three years to be diagnosed, visiting at least two consultants and spending 10 days in hospital before they receive a correct diagnosis,"[5] he continued.

"Greater awareness in the medical profession, especially at GP level, as well as the general public, would substantially reduce both the financial and emotional cost associated with this condition. Patients unfortunately arrive in A&E as emergency cases with DVT or pulmonary embolism, and – in the case of arterial clots – may present with stroke or heart attack. The figures are staggering," he commented.

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A conservative estimate of people at risk from Hughes Syndrome is 1% of the population – greater than the number of people that suffer from Parkinson's disease or Multiple Sclerosis (MS). One study has even indicated that it could be as high as 2% to 4%.

Prof. Hughes explained that Hughes Syndrome is more common in women (2:1), although the gender difference is less apparent when compared to Lupus (9:1). Often there may be a family history of autoimmune diseases (such as thyroid problems or Lupus, for example), while a strong family history of migraines for many patients also points towards genetic influences.

"At the clinic, we see families with four to six members of the family with Hughes Syndrome

and, in one family with 14 siblings, half had the condition," said Prof. Hughes. "Not all patients will have a family history, but the numbers are such that we believe that genetic influences are important."

"Asking patients the right questions is key," he continued. "Clinicians should ask if they have aunts with thyroid or MS, for example. One of my patients revealed that their cousins believed they were developing Alzheimer's, when in fact they were young, female and probably had Hughes."

Clinical effects of Hughes Syndrome

Patients may initially attend their GP with a wide range of general symptoms – ranging from headaches or migraine and memory loss, to Multiple Sclerosis-like features, balance problems and fatigue.

However, the condition has importance for a multitude of specialties – including: emergency medicine, neurology, cardiology, rheumatology, orthopaedics, gastroenterology, haematology, nephrology, ENT, dermatology, psychiatry and tissue viability. (See Table 1 for a detailed list of clinical presentations.) In fact, every organ can potentially be affected, Prof. Hughes explained.

The brain

In the brain, the effects may cause memory loss, migraine, headaches, movement disorders, epilepsy, transient ischaemic attacks or stroke.

"A study was conducted some years ago, when I was at St Thomas' Hospital in London, in conjunction with a group in Barcelona, which evaluated patients at a stroke clinic. The study found that 7% were positive for Hughes Syndrome. A group in Rome also looked at young strokes, under the age of 45, and found that around 20% were positive for Hughes Syndrome," said Prof. Hughes.

"Some of our patients with brain symptoms also feel that they are getting Alzheimer's as they have memory problems – such as recalling names, for example. The memory loss can be mild and patients often describe being 'the joke of the family'. However, once you put them on aspirin or warfarin the difference is usually significant – patients tell you that the 'fog' has lifted and they feel mentally 'sharper'. I use the analogy of petrol, when explaining the condition to patients – if the mixture is too rich, not enough gets through to the engine which causes it to 'stutter'."

Patients may also experience symptoms such as pins and needles, peripheral neuropathy, balance impairment, and/or visual disturbance. Movement disorders can also be a feature, with some patients exhibiting "jerks and twists" or even St Vitus Dance.

Given the similarities between MS and Hughes Syndrome, research is underway to examine the possibilities of misdiagnosis in some MS patients. In fact, Prof. Hughes reported that up to one third of his patients at his clinic had a previous diagnosis of MS mooted.

One patient, for example showed progressive weakness, abnormalities to

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the spinal cord on MRI, difficulty walking and bladder control – all pointing to MS, but subsequently tested positive for Hughes Syndrome. His condition improved with treatment on warfarin and, after eight years, the patient showed no further deterioration.[6]

"We are still some way from knowing how many patients attending MS clinics around the world have Hughes Syndrome, but, since the condition can 'mimic' MS and Hughes can be treated, it would make sense to perform a blood test," he advised.

Seizures can also be a feature and it has been observed that up to 20% of young people with "idiopathic" epilepsy have Hughes Syndrome.[7]

Other organs

In the heart, patients may experience angina, murmurs, and even valve problems. "If a young person presents unexpectedly with a heart attack, you should be on the alert as to whether or not he or she may have Hughes Syndrome," Prof. Hughes warned.

He added that a patient's kidneys can also be affected, commenting: "Blood pressure may rise, or the arteries in the abdomen may be affected – resulting in abdominal angina. This often presents as abdominal pain after a meal, caused by insufficient circulation to the gastro-intestinal tract."

Hughes Syndrome can also cause Raynaud's Syndrome – a condition in which blood is prevented from reaching the extremities of the body, mainly the fingers and toes, on exposure to the cold. Other issues can include: a drop in blood platelet count, clots in the eye, and recurrent leg ulcers.

"Leg ulcers, for example, are a huge socio-economic issue," Prof. Hughes pointed out. "Patients can spend weeks in hospital at great cost to the NHS and the economy – not to mention the human cost. One of my patients, a ballet dancer, found that she had to halt her career due to recurrent leg ulcers. Immediately after being put on blood thinning treatment the ulcers healed. There may be a large subgroup of patients with chronic leg ulcers out there, due to 'sticky blood', who may benefit from anticoagulation."

In orthopedics, idiopathic fractures have also been linked to Hughes Syndrome,[8] while, in dermatology, patients may present with livedo reticularis (described by one of Prof. Hughes' patients as "corned beef skin"). Menieres is another clinical presentation that is often linked with Hughes Syndrome – patients may experience balance problems, tinitus and/or deafness caused by an infarct in the inner ear.

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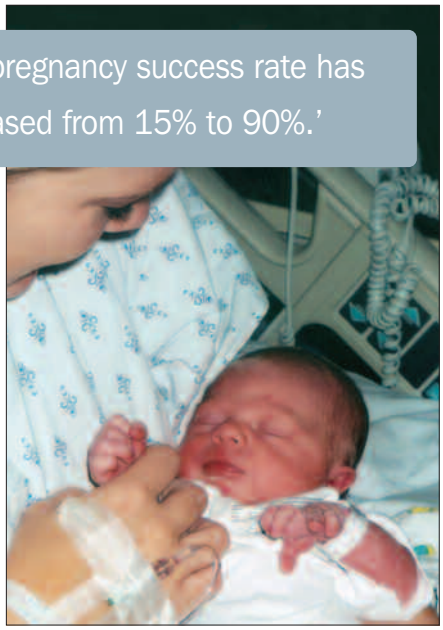

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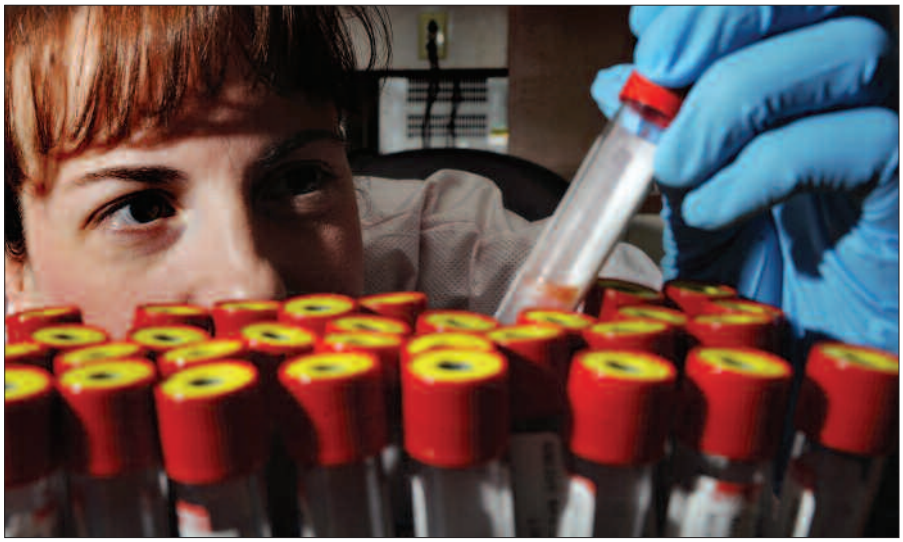
Some Hughes Syndrome patients may also present with other autoimmune disorders – the two most commonly associated being thyroid problems and Sjogren's Syndrome. The latter is characterised by dryness and irritation of the eyes, dryness of the mouth, together with a tendency for aches and pains.



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Miscarriage

Hughes Syndrome is also recognised as the leading cause of recurrent miscarriage. Placental infarction is believed to be the main factor, although there is also some evidence of an inflammatory process having a contributing role. In addition, there is further suggestion that problems with implantation and/or very early pregnancy loss may be a cause of infertility in patients with the condition, and there is now a move towards testing for Hughes Syndrome in the IVF sector.

Catastrophic APS

"A rare complication, and one of the most feared, is 'catastrophic APS' – where a person is fine one moment, then suddenly everything starts clotting and they end up on ITU. It is a nightmare scenario," said Prof. Hughes. The clots may involve any or all of the vital organs – including the lungs, liver, the adrenals and the brain.

He explained that, although the triggers are not fully understood, there is some evidence to suggest that a virus, sore throat or chest infection may start this process.

Risk factors

While infection is known to add to the risk of thrombosis in patients with Hughes Syndrome, there is also evidence to suggest that diet and lifestyle may affect outcome. Smoking, the Pill and long haul flights have been triggers in some cases, but diet is also thought to be an influential factor.

A study comparing Indian and Arabic populations found the same incidence of antiphospholipid antibodies, but twice the incidence of blood clots in the Arabic population.[9]

"The suggestion is that perhaps the healthier lifestyle and vegetarian diet of the Indian population made a difference," commented Prof. Hughes.

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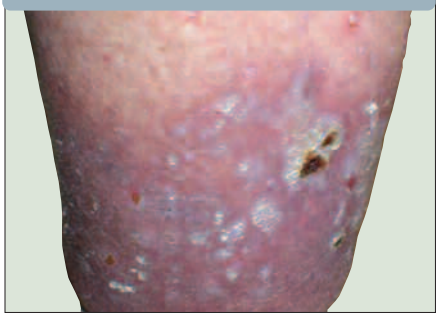

Testing and treatment

Hughes Syndrome can be detected with relatively simple and cheap blood tests including: aCL (anticardiolipin), LA (Lupus anticoagulant), and some units are now doing a third test – the anti-beta2-glycoprotein1. Protection is usually provided by administering low dose aspirin or warfarin, while low molecular weight heparin may be substituted during pregnancy.

Not only is testing inexpensive, therefore, but anticoagulation is cost-effective when compared to the cost of treating more serious, long-term complications associated with Hughes Syndrome. If patients test positive, there is a very high chance of a clot or miscarriage if they are not treated.

"Ten year studies of people who have tested positive and not been treated have shown that up to 50% will get a clot within the first decade," Prof. Hughes explained.

Currently, there is debate over whether it is preferable to treat with low dose aspirin or low dose warfarin and research is underway in this area, although Prof. Hughes pointed out that it can be hard to recruit for trials, as many patients prefer not to take warfarin. Getting the INR right can also be challenging, and he therefore encourages patients to get their own INR testing machine.

However, there is also desperate need for a new anticoagulant, in his view. He revealed that there are some promising solutions in tablet form on the horizon, based on heparin, which eliminate the inconvenience of an injection. One of these is undergoing the last stages of trials to establish efficacy in prevention of DVT in knee replacement. In addition, the potential of immuno-suppressants is also being explored.

"Rituximab has been used for some of our worst cases – it has lowered the antibody level and there appears to be less thrombosis, giving some grounds for optimism," he commented.

Unfortunately, one of the barriers to obtaining treatment is the fact that patients continue to report difficulty in persuading their GP to refer them for tests. It can be a long and frustrating battle – even for well-informed patients where there is a family history.

In Prof. Hughes' view, anyone experiencing frequent headaches or migraine, visual disturbance, memory loss or abnormal neurological features should be automatically tested – in addition to women who have experienced a single miscarriage; and following stroke, DVT or heart attack. Testing should also be considered where there is a strong family history of migraine and thrombosis.

In the NHS, cost is often cited as a reason for delaying routine testing in women who experience miscarriage, and calls for testing to be extended to form part of a national stroke strategy are not yet implemented.

"People advocate that patients should

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'People advocate that patients should have had at least three miscarriages before testing is considered. If my daughter had just one miscarriage, I would want them to be tested for Hughes Syndrome. The test should be part of routine pregnancy screening.'

have had at least three miscarriages before testing is considered. But it is appalling to expect a woman to face multiple miscarriages when this could be prevented. If my daughter had just one miscarriage, I would want her to be tested for this," Prof. Hughes asserted.

He believes that the test should be part of routine pregnancy screening and pointed out that syphilis is currently tested for, which has a very low yield in comparison to Hughes Syndrome.

"Others disagree on economic grounds, stating that the number of borderline positive results is an issue. However, in my view, women should be treated during pregnancy if they are borderline positive," he commented. "The pity of it is that Hughes Syndrome is easily diagnosed and very treatable," Prof. Hughes continued. "The pregnancy success rate at our clinics has increased from 15% to 90%."

Prof. Hughes said that he does not advocate population screening for all, but added that "it is interesting to note that population screening for cholesterol has been introduced, yet the link with disease is less strong than that found between Hughes Syndrome and thrombosis.

"For the sake of a test that costs a few pounds we could prevent recurrent miscarriages, strokes and heart attacks. In the UK, it has been estimated that stroke is number one in terms of national medical expenditure, accounting for over 10% of the annual NHS budget. The cost savings, for this alone, would be significant," he concluded.

- For more information about Hughes Syndrome, visit www.hughes-syndrome.org

Currently head of the London Lupus Centre at London Bridge Hospital, Professor Graham Hughes has an international reputation for his research in the diagnosis and treatment of Lupus and related autoimmune conditions. His research into Lupus led to what is perhaps the most exciting of his discoveries – now widely known as Hughes Syndrome. It has been described as "one of the most important new diseases of our time" and, in 1992, he and his team received the highest award in international rheumatology – the ILAR prize (International League Against Rheumatism) for their work in this area.

Table 1: Clinical effects.

Vein thrombosis
DVT, pulmonary embolism, "Economy Class Syndrome" or thrombosis on the pill.
Artery thrombosis
E.g. limb pain, organ thrombosis.
Pregnancy
Recurrent miscarriage, including early and late pregnancy loss.
Infertility.
Intra-uterine growth retardation.
Brain
Headache and migraine
Stroke and TIA.
Memory loss.
Balance disorder (and sometimes hearing impairment).
Seizures.
"Atypical" Multiple Sclerosis.
Speech disturbance.
Movement disorder, including Chorea (St Vitus dance).
Absences.
Severe dementia (rare: untreated cases).
Heart and lungs
Heart attacks, murmurs.
Lung thrombosis (pulmonary embolism).
Shortness of breath.
Pulmonary hypertension (raised pressure).
Valve failure (rare).
Angina.
Eyes
Sudden visual loss (clots around the eye).
Loss of part of field of vision.
Dry eyes (Sjogrens' Syndrome).
Skin
"Blotchy" circulation ("livedo").
Skin ulcers and nodules.
Cold circulation.
Kidney
Thrombosis in artery or vein.
Raised blood pressure.
Liver
Liver thrombosis.
Blood
Low platelets counts.
General
Fatigue.
Aches and pains.
"Catastrophic" APS (widespread sudden thrombosis).

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