



## UNDERSTANDING CVID

### Introduction

Most of us take it for granted that our immune systems will fight off infection and keep us healthy. People with defective immune systems know only too well that an underactive immune system means a lot of ill health and even the risk of dying from infections which are easily eliminated by a “normal” person’s immune system.

Common Variable Immunodeficiency (CVID) is a group of conditions in which the patient is unable to produce sufficient antibodies - substances in the blood that identify germs that have previously infected the person. As a result, the patient has an under active immune system (immunodeficiency) which provides poor protection against repeated infection mainly by bacteria, but also viruses, parasites and fungi. CVID affects approximately 1 person in 30,000, but overall one or another form of primary immunodeficiency may affect up to 1:2,500 individuals.

CVID is a group of up to 30 different disorders, which appear to have different causes. Most types of CVID are primary immunodeficiencies; that is, they don’t appear to have an external cause such as a virus or surgery. However, many secondary (externally caused) forms of immunodeficiency have a similar pattern of illness and treatment to CVID and much of the information in this leaflet may also apply to them. As research continues, we hope to gain a greater understanding of the causes of the different types of CVID, and this may lead to new treatments for certain types, such as genetic therapies which effectively cure the disorders.

### Overview of the Immune System and CVID

The immune system protects us from infection and cancer in 3 main ways:

- Physical barriers (intact skin, normal flow of urine, saliva, tears)
- Basic or “innate” immunity
- Specialised or “adaptive” immunity

CVID affects the last group, which is known as adaptive because it changes with our experience of the world around us. When we get an infection it is able to remember this and fight it more effectively the next time around. For people with CVID the hallmarks of frequent and severe infection therefore make sense, their immune system has not properly remembered how to defend them against repeat infection.

The adaptive immune system is made up of white blood cells called *lymphocytes*, which are further split into *T* and *B cells*. The B cells make antibody (immunoglobulin or Ig) and the T cells help fight virus infections and regulate the immune system. In CVID the B cells do not produce proper levels of antibody (IgG, IgA or IgM which are the main 3 classes of Ig) but we do not know if this is because the T cells, B cells or something else is ineffective. A few very similar disorders, such as X-linked agammaglobulinaemia, are due to changes in single genes but it is likely that in the various types of CVID several genes are involved.

Some patients with CVID or related diseases are described as having either agammaglobulinaemia, which means an absence of antibodies, or hypogammaglobulinaemia, which means low levels of antibodies. Other people will not respond effectively to certain types of bacteria even though they have good levels of antibody overall; these individuals may be told they have a "functional antibody deficiency".

Young children (up to school age) may suffer more infections than their peers because their immune system is slow to develop; this is known as transient hypogammaglobulinaemia. Fortunately most of these children get better quite quickly and will only need to take preventative antibiotics. However, a small minority need immunoglobulin treatment. This can usually be stopped at some point and the function of their immune system re-assessed to see if they still need this treatment.

Other disorders related to CVID include agammaglobulinaemia arising from radiation exposure and having a thymectomy (removal of the thymus gland); this has very similar symptoms and treatment, but is known as Good's Syndrome and is a secondary immune disorder.

## Diagnostic Process

Diagnosis can take many years because CVID is relatively rare and even when low immunoglobulins are found it may take some time for the significance of this to be determined. Doctors find it hard to recognise "too many" infections and many patients have non-specific symptoms, like weight loss, that make the diagnosis hard to pin down. The length of time CVID takes to diagnose causes many patients a degree of anger, and the management of the diagnostic process relates heavily to how they feel about their diagnosis when it is made.

## History

As with other PIDs the common feature is of frequent and/or unusual infection including:

- Sinusitis
- Ear infections such as otitis media
- Throat infections such as tonsillitis or laryngitis
- Chest infections such as bronchitis, pneumonia or pleurisy
- Stomach and intestinal infections such as ulcers, gastritis or giardiasis (a parasitic infection)
- Skin infection, such as abscesses, boils, tendency to get infections in scrapes and cuts or fungal infections
- Oral ulcers
- Eye infections such as conjunctivitis or styes

Autoimmune diseases, joint and bowel problems, and occasionally cancers can be related to CVID.

## Investigations

For most patients with CVID the patient's story when taken by an experienced specialist "says it all", but doctors like tests and immunologists are no exception! The basic tests for CVID are blood tests to look for antibody levels and the number and function of T and B lymphocyte white blood cells. Some immunologists may want to exclude infection by HIV in the diagnostic process, although you should take advice on the best way of taking an HIV test as some insurance companies discriminate against people who have had such tests; tests taken in a sexual health clinic cannot be reported to anyone, and so this may be the best solution for some patients. In addition the team may want to take X-rays, CT body scans, samples of any infected body fluids (e.g. pus or diarrhoea) and ultrasound scans of immune system organs such as the spleen.

Patients who have had multiple chest infections may have permanent damage to the tubes in the lungs, known as bronchiectasis. This can show up as shadows on a chest x-

ray which may be mistaken for tuberculosis; doctors will want to rule this out by testing for tuberculosis.

Computer Tomography (CT) scans may be more useful than chest x-rays in detecting lung problems in patients with CVID. In a CT scan, the scanner rotates around the patient, building three-dimensional image which helps the doctor to see more detail.

Tests may be intensive at the beginning, but once all the information is in, monitoring is usually by infrequent blood tests and for some people annual scans or tests of breathing function.

## **Treatment**

The mainstay of treatment for CVID is replacing the missing antibodies with immunoglobulin replacement therapy taken from a pool of healthy blood donors. Immunoglobulins may be administered intravenously (dripped into a vein through a needle in the arm or hand) or subcutaneously (injected under the skin in the lower stomach or thighs). This treatment is usually needed every week for subcutaneous therapy or every 2-4 weeks for intravenous therapy depending on the individual.

Additional treatments may include antibiotics to prevent infection, physiotherapy, treatments for specific conditions such as arthritis or diarrhoea.

## **Vaccination**

Vaccination is an important part of modern life, and parents should ensure that their children are vaccinated appropriately. However, patients with CVID have special requirements which are important to bear in mind.

Any patient with an immunodeficiency should avoid receiving any live vaccine. In live vaccination, the agent in the vaccine which is used to promote antibody production is a weakened version of the germ which the patient is being vaccinated against. A person whose immune system is defective is as likely to be infected by even a weakened version of the pathogen and so should be avoided. Examples of live vaccines include the BCG vaccination, polio vaccine and "Flu Mist", an influenza vaccine which is delivered through a nasal spray. Patients, or parents of patients, should always seek the advice of the patient's immunologist before accepting or declining the vaccine.

Recent research by the Royal Free Hospital indicated that having the annual 'flu vaccine may have a positive effect in some patients, and the consensus is that the decision to have the jab is down to the patient.

## **Travelling with CVID**

Patients with CVID who are travelling between infusions in the west with high-quality clean water supplies are unlikely to have any serious problems. However, the *Travel advice for patients with PID* leaflet may help make life less stressful.

## **Living with CVID**

People diagnosed with CVID face many challenges, ranging from adapting to the diagnosis through to working or going to school.

Anybody who receives a chronic diagnosis is likely to feel a rush of mixed emotions as they get used to the fact that they will live with this for the rest of their lives. Adapting to long-term diagnoses has been likened to grieving; both involve adapting to major life changes and hence have similarities in the process.

For more information see *Living with PID*.

## **Children with CVID**

Obviously, finding out that a child has CVID can be a real shock and parents are likely to go through the grieving process. They should be assured that immunoglobulin therapy is likely to ensure they can live a relatively normal life; children pick up on their parents' emotions and worrying about it will teach the child to be scared and worried about this aspect of their lives.

For more information see *Children with PIDs and Immunoglobulin Replacement Therapy*.

## **Conclusion**

The future for CVID is bright: research into CVID is continuing and patients can look forward to advances in diagnosis and treatment in the future. The PiA is investing money into research projects and providing support to CVID patients all over the UK.

CVID can be a life-changing diagnosis, but effective management using appropriate treatments (such as immunoglobulin therapy) means that people with CVID live relatively normal lives. We do have to make adjustments, but often these are minor sacrifices which are more than outweighed by the benefits experienced. Above all, we remember that we are in control of our disease, and that our disease doesn't control us.

**Written by David Waldock (PiA member)**

**Edited by Dr Matthew Buckland and Prof Andrew Cant (Immunologists)**

## **CVID – Two Patients' Perspectives**

### **I'M A HYPOGAMMAGLOBULINAEMIC!**

It's very hard to establish when it all began. My Immunology consultant would certainly like to know! All I can point to is five small outbreaks of shingles within 36 months and that for at least two years I walked around with a constantly painful, very swollen right ankle, had two sets of traction for back pain and umpteen prescriptions for sinus trouble. A wart suddenly became a rodent ulcer and had to be cut out. I was tired all the time. I thought, and still think of myself as a robust and healthy person, particularly as I am carer for my disabled husband, so I took all these in stride and accepted that the ankle pain was arthritis owing to many bad sprains in childhood, the back trouble was attributable to over-exertion in our large garden and the sinusitis merely an on-going problem which I've had to a much lesser degree throughout my life. As I was 52 at this time, I attributed the tiredness to the likely onset of menopause, but nobody ever explained the shingles!

Everything came to a head when my husband and I returned by air from a holiday in May 2002. I had a runny nose again and while waiting for our luggage, I sneezed and felt mucus blow into my right ear. I've never suffered from earache and assumed the blockage would clear. Ten days later I was admitted to hospital in agony. I'd already had two antibiotics and ear drops, but nothing touched the infection. Morphine just about kept the pain under control until my right ear was drained under general anaesthetic and a grommet inserted in the eardrum. I was sent home with a carrier bag full of antibiotics, nose drops, ear drops, painkillers and a nasal spray, but I still had to be rushed back into hospital nine days later with the same problem in the other ear! I had the same treatment, was discharged, and spent the next month trying to get somebody to listen when I told them that I was losing my hearing. By the time I saw the ENT consultant I could hardly hear him at all. He sent me straight for an audiology test and was appalled by the results. He told me that I would need two hearing aids and that he was thinking of referring me to the department of immunology. I felt too ill to even ask why!

I spent three months wondering why I wasn't recovering from such minor surgery. My husband was almost frantic with worry and our daughters were very upset. I had conjunctivitis which wouldn't clear up, to the degree that I started wearing an eye-patch on my right eye because it was so painful and looked like a ripe cherry tomato! I felt I should do what I could for myself so arranged an eye test, a mammogram and a smear test, but nothing revealed a problem.

I was seen by a consultant immunologist on a Tuesday in October. It was a great relief to finally talk to somebody who could draw out of me all those things which had seemed totally unrelated and who seemed to think he would be able to make sense of them. I had physical examination then had 9 vials of blood drawn for tests and went home. The consultant 'phoned me just two days later to say that he knew what was wrong and would I please come back to see him again the following Tuesday. He told me enough to stop me worrying and when my husband and I saw him, his explanation was clear. The test result that made the most impression on me was the graph showing that I had **0.46 of one percent** of my immune system still functioning. No wonder I'd been feeling so rotten except when on antibiotics! I'd never heard of hypogammaglobulinaemia! I'm no wiser about *why* I developed it even now. There is no genetic trace to be found in the four generations of family I can look back over.

Within a fortnight I had my first infusion of Octagam. It took six and a half hours because of the antihistamine and hydrocortisone which preceded it and to which I reacted. I had to have both again three weeks later! I only had four infusions before the specialist nurse at the unit gave me another blood test because I said that I felt like a toy which had run down by mid-way through the third week. The result showed I needed fortnightly infusions. In the meantime, I had had a CT scan of my sinuses and temporal lobe, lung function tests, and my ENT consultant had agreed to hand over my care to the immunology department which maintains its own ENT specialist. I had a lung x-ray and was told I had some bronchiectasis, but nothing to worry about, then my thorax was scanned.

My hearing had been very acute and I grieved more over its loss than over my diagnosis. A month of two lots of antibiotics and nasal drops regained me more hearing than I had ever hoped for although the two comfortable hearing aids I wear are still necessary. I never felt the anger that others have described to me, or queried 'why me?', maybe because I felt MUCH better than I had for more than two years, to the extent that I looked back and wondered why I didn't realise sooner how ill I was. Many people have since told me a similar story: even if their GP was helpful, he/she would never have put the necessary pieces of the puzzle together to arrive at the right diagnosis, because immunology is not well taught to our young doctors and PIDs are rare.

Nowadays I have lots of energy but I don't think my nose will ever be completely clear. It's tolerable and I function well on a 6 weekly rotation of prophylactic antibiotics. I have no trouble with the anti-inflammatory drug I take 3x daily. This year I have been taught to administer my own weekly IG infusion subcutaneously at home, using Subcuvia in a syringe driver. This means that the only trips I have to make to the hospital are to see my consultant.

In many ways I feel very lucky. I happened to be in the right place at the right time for someone very clever to realise that there was something going on with which he couldn't deal himself, but put me in a position to see someone who could.

**Gillie Moloney (PiA member)**

### **HAVING GOOD'S SYNDROME – A personal view**

In 1992 I hadn't been well, having a persistent dry cough, which was so usual I had begun to not even notice I was coughing, except that my wife noticed and was concerned. I saw my GP and he thought it was maybe asthma, prescribing dilators and puffers, all to no avail.

Things came to a head a few weeks after we returned from a trip to Mexico, when I started to feel very unwell, finally collapsing on a Sunday afternoon. Fearing I had picked up something abroad my wife telephoned the London Tropical Diseases Hospital and they told her to get me there as soon as possible.

On admission I was examined and told I had either TB or Malaria and I needed to be in an isolated room. There I stayed for three days, still feeling very sick, but not testing positive to the suspected conditions. Finally a doctor picked up on my cough and sent me for a chest x-ray, when it was found that I had a large mass in my chest, a shadow that showed something between my heart and lungs. The doctor guessed it was either lymphoma or thymoma and ordered a biopsy, which was done whilst I was moving in and out of a CT Scanner.

The biopsy revealed that I had thymoma, and the recommendation was that I should have it surgically removed, and that this was the probable reason for my cough.

I had it removed six weeks later, a procedure known as thymectomy, and began a long recovery from a very severe operation. A common after effect of having a thymectomy is Myasthenia Gravis, a neurological condition that can cause its sufferer to have a very low standard of life. Fortunately for me I did not have MG, and also fortunately my thymoma was benign and I didn't need any follow-up treatment. However it was clear that my cough had not gone, in fact it was back two days after surgery, and now coughing was an absolute hell. As I recovered from the surgery it also became clear that things had actually become much worse, I was now suffering from incredible sinusitis too, the pain in my head was persistent, and the cough was getting worse.

To cut a long story short, after an abortive attempt to clear the sinusitis by sinus surgery I finally met up with some doctors who thought that maybe it was my immune system that should be investigated, and it was soon discovered I was immunodeficient.

My initial diagnosis was CVID, and I was treated by having two injections of concentrated gamma globulin intra-muscularly every four weeks. About that time I discovered the antibiotic Septrin, and took this every day, and found my cough disappeared and the sinusitis abated but not before it had damaged my left ear and given me tinnitus, which I still have. Two years on and it was decided that I was a good candidate for intravenous gammaglobulin therapy, a treatment I have had every three weeks ever since.

However in the course of the last ten years it has been explained to me that thymoma and immunodeficiency are linked, and that although I am treated as a patient with CVID, I in fact have Good's Syndrome. People with CVID have a very rare condition among the general population and people with Good's Syndrome form a tiny percentage of them, making me and other Good's Patients terribly unusual!

My treatment regime has been very successful and I lead an active and productive life. As with all CVID patients I have the occasional breakthrough infection that quickly pulls me down, but treated with the right antibiotic I am soon well again.

**John Satchell**



**PIA Alliance House 12 Caxton Street London SW1H 0QS**  
**T 0207 976 7640 F 0207 976 7641**  
**E [info@pia.org.uk](mailto:info@pia.org.uk)**  
**W [www.pia.org.uk](http://www.pia.org.uk)**

Medical information published by the PiA is approved by our Medical Advisory Panel. However, it is intended for general guidance only, and should not be used in place of the personal consultation needed with your physician.