

Sudden Sensorineural Hearing Loss and Antiphospholipid Syndrome

The antiphospholipid syndrome is the association between the presence of antiphospholipid antibodies, thrombosis and/or pregnancy morbidity and mortality. This report presents two cases of antiphospholipid antibodies and sensorineural hearing loss and discusses the probable causative link. We recommend that patients presenting with sudden sensorineural hearing loss are investigated for evidence of antiphospholipid antibodies. Life long anticoagulation is necessary to prevent life threatening thrombotic or thromboembolic events.

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The antiphospholipid syndrome (APS) is an acquired disorder resulting in hypercoagulability. It is defined by the presence of antiphospholipid antibodies in association with arterial or venous thrombosis and/or pregnancy morbidity and mortality.¹ The assays for antiphospholipid antibodies include both the lupus anticoagulant and anticardiolipin antibodies. APS occurring in the absence of other autoimmune disorders is known as the primary antiphospholipid syndrome. If APS occurs with another autoimmune disorder, usually systemic lupus erythematosus, then it is known as secondary APS. There is an increasing recognition in the literature of an association between APS and sudden sensorineural hearing loss.² We present two patients who presented with sudden sensorineural hearing loss (SNHL) and fulfil the laboratory criteria for primary APS,¹ and review the literature.

Case Report 1

Clinical presentation

A 52-year-old man presented with a history of sudden hearing loss. He was a regular recreational runner. Three months previously whilst running he became aware of a buzzing noise in his right ear. Within minutes he developed a complete hearing loss affecting the right ear, which failed to recover. He also complained of transient vertigo and a feeling of pressure on the right side of the head which radiated to the back of the neck. The vertigo abated quickly but the hearing loss remained. He denied any previous symptoms of joint pains, skin rashes, mouth ulcers or general malaise. There was a past history of a left cerebral abscess of unknown aetiology at 24 years of age while working in the tropics. Tonic-clonic seizures after this episode were well controlled with carbamazepine. An ENT opinion was sought by the patient's General Practitioner.

On examination the tympanic membranes were pristine. Neuro-otological examination revealed a loss of auditory acuity in the right ear but normal hearing in the left ear. Pure tone audiometry confirmed a total sensorineural hearing loss affecting the right ear. Pure tone audiological thresholds of the left ear were normal. Tympanometry revealed normal compliance of the tympanic membranes. Examination of the other cranial nerves revealed long-standing changes of a right afferent pupillary defect and a right homonymous hemianopia, secondary to neural damage associated with his previous cerebral abscess. There were no stigmata of systemic lupus erythematosus or any other connective tissue disorder. An MRI scan of the brain showed a large area of cortical and white matter destruction of the left parietal and

occipital lobes consistent with his previous cerebral abscess. The internal auditory canals were symmetrical and of normal diameter with no space occupying lesion seen in either cerebellopontine angle.

Laboratory investigations

The full blood count and ESR (13 mm/hr) were within normal limits. A coagulation screen showed an INR of 1.00 (normal ratio 0.80 - 1.10) and APTT of 0.96 (normal ratio 0.80 - 1.20). Serum electrolytes were normal. Plasma homocysteine levels were 6.6 µmol/L (normal 10.0 - 17.0). Total triglyceride levels were 0.72 mmol/L (normal (0.00 - 2.30 mmol/l)). Total cholesterol level (non-fasting sample) was 5.5 mmol/L.

The dilute Russell's viper venom test was used to assay for the lupus anticoagulant. The initial assay was prolonged at a ratio of 1.39 (range 0.9 - 1.1), and proved positive, when phospholipid was added, by correcting to within the normal range at 1.02 (range 0.9 - 1.1). Testing on two further occasions two months later gave similar results. Anticardiolipin antibodies, IgG and IgM levels tested by ELISA were within clinically normal limits. Serological investigations revealed no evidence of antinuclear antibody, anti-neutrophil cytoplasm antibody or antibodies to extractable nuclear antigens.

With a presumed thrombotic cause of SNHL and laboratory investigations which fulfil the criteria for diagnosis of antiphospholipid syndrome, he was diagnosed as having primary antiphospholipid syndrome. In view of the possible risk of recurrent thrombosis, the patient was formally anticoagulated with warfarin indefinitely to maintain an INR between 3.0 and 4.0. He remains systemically well but he has a persistent profound sensorineural hearing loss affecting the right ear.

Case Report 2

Clinical presentation

A 56-year-old man presented with a history of sudden onset of left sided hearing loss. This was preceded by occasional dizzy spells associated with a slight cold a few months prior to presentation, but without a postural component. He had also experienced occasional tinnitus on the left prior to presentation.

He had a brief period of mild to moderate noise exposure whilst working for one year in a shipyard in Japan, 30 years previously but this was not thought to be significant, nor associated with tinnitus or temporary hearing loss at the time.

General examination was unremarkable, with no stigmata of autoimmune disease and no neurological deficit. He was a moderate drinker and heavy smoker, with an alcohol intake of 22 units per week and smoked 20 to 30 cigarettes a day for the last 30 years. There was no previous thrombotic history.

Otological examination revealed normal tympanic membranes and tuning fork responses and tympanometry showed normal compliance of the tympanic membranes. Pure tone audiometry showed asymmetrical bilateral high tone sensorineural hearing loss on both sides, much more severe on the left. Acoustic impedance measurements were normal.

An MRI scan of the brain was unremarkable.

Laboratory investigations

The full blood count was within normal limits. ESR was normal at 2 mm/hr. Total cholesterol level (non-fasting sample) was 3.6 mmol/L with HDL 0.87 mmol/l, LDL 2.07 mmol/l and triglycerides 1.45 mmol/l. Plasma

homocysteine levels were normal at 8.0 $\mu\text{mol/L}$ (normal 10.0 – 17.0).

He had a lupus anticoagulant test positive with the DRVVT ratio prolonged at 1.18 (range 0.9 - 1.1), and, correcting to 1.08 (range 0.9 - 1.1) with phospholipids on 2 occasions. Anticardiolipin antibodies tested by ELISA were within normal limits.

An autoantibody screen was negative which included antinuclear antibody, anti-neutrophil cytoplasmic antibody and antibodies to extractable nuclear antigens.

The diagnosis of primary APS on the basis of presumed thrombotic cause of SNHL was made and he was formally anticoagulated with warfarin to maintain an INR between 3.0 and 4.0 indefinitely. Unfortunately he continued to smoke, although reduced the number to 10 per day. Eight years later he remains on warfarin with the addition of aspirin due to coronary vascular disease in the form of angina. He has had no additional thrombotic episodes, and although sensorineural hearing loss prevails, it has not deteriorated.

Discussion

The antiphospholipid (or Hughes') syndrome is the association of thrombosis, pregnancy morbidity and mortality with antiphospholipid antibodies.¹ Patients with APS present with multiple and diverse clinical features due to local thrombosis. Histological examination of the clot reveals an organised thrombus of platelets and fibrin without evidence of inflammation. There is no evidence of vasculitis. This differentiates APS from SLE and other autoimmune disorders where thrombosis is a result of inflammatory changes in the vessel wall. Thus, the management of APS is based on anti-thrombotic, rather than anti-inflammatory, treatment.

The antiphospholipid antibodies are a diverse group of antibodies directed at various epitopes. The routine laboratory assays in which they are detected are the lupus anticoagulant assay and the anticardiolipin antibody by ELISA. An individual patient may have only one of these two types of antiphospholipid antibody, therefore both assays must be performed to detect all individuals with antiphospholipid antibodies. Diagnosis relies on the persistence of antiphospholipid antibodies on two separate occasions more than 6 weeks apart at the time of patients' presentation 1, which has since been increased to 12 weeks, 3 in conjunction with evidence of thrombosis. The presence of antiphospholipid antibodies predisposes to both arterial and venous thrombosis. Vessels of any size may be affected and no part of the circulation is spared.⁴ Thus patients can and do present to any specialty with the complications of thrombosis. e.g. stroke to the general physicians, retinal vessel occlusion to the ophthalmologist, renal vein thrombosis to the nephrologists, placental infarction to the obstetrician, pulmonary emboli to the respiratory physician, peripheral vascular disease to the vascular surgeons, Budd-Chiari syndrome to the hepatologist etc. Clinical manifestations do not seem to differ between anticardiolipin antibody and lupus anticoagulant but in general, patients with the highest levels of anticardiolipin antibodies, particularly of the IgG isotype, have the severest disease,⁵ and those with lupus anticoagulant are more prone to thrombosis.⁶ Thrombosis tends to recur in the same vascular bed.⁷

The incidence of idiopathic SNHL is approximately 20 out of 100 000 people per year, and is classified as idiopathic after careful exclusion of the many causes of SNHL. The site of the lesion resulting in sensorineural deafness can be predominantly localised to the cochlear, but may also be caused by retrocochlear lesions.

There has been recent interest into the pathogenesis of idiopathic or sudden SNHL. Several hypotheses prevail, thrombosis, autoimmune disease and viral infection. SNHL has been linked with autoimmune diseases, in particular; systemic lupus erythematosus (SLE) for some years. Much of the evidence linking the immune system with cochleovestibular dysfunction is indirect, largely as an interpretation of case reports and response to immunosuppressive treatment.

In support of a thrombotic cause of SNHL, small infarctions of cochlear tissue have been found in subjects with multifocal microangiopathic encephalopathies and deafness.⁸ In addition, *in vivo* animal studies have showed vascular obstruction in the inner ear resulted in reduction of intracochlear oxygenation and ultimately significant loss in the auditory response.⁹ Confirming thrombotic occlusion in cases of SNHL however, is obviously impractical owing to the location of the cochlea within the temporal bone. Marcucci *et al.*¹⁰ studied a number of inherited and acquired thrombophilic risk factors including anticardiolipin antibodies and lupus anticoagulant in 155 patients with idiopathic SNHL within 30 days of onset. They found 20% had a positive anticardiolipin antibody and 8.4% with a positive lupus anticoagulant. Positivity for anticardiolipin antibody was found to be an independent risk factor for idiopathic SNHL. A number of thrombophilic risk factors were investigated, of those total cholesterol, PAI-1 and homocysteine levels were also found to be independent risk factors after multivariate analysis. This indirectly supports the role of vascular occlusion in the pathogenesis of sudden SNHL. This case control study is based on one positive anticardiolipin antibody or lupus anticoagulant, which makes it impossible to determine the prevalence of APS in the study population.

Many of the cases previously described in the literature detailed below describe elevated antiphospholipid antibodies, in association with SNHL but the diagnosis of APS has not been contemplated nor fully investigated. We suspect there would be a high prevalence of APS-both primary and secondary in the following cohort of patients. Hisashi *et al.*¹¹ were the first to demonstrate an association between progressive sensorineural hearing loss in patients with SLE and anticardiolipin (antiphospholipid) antibodies. They reported the case of a 15 year old female with SLE who developed bilateral brainstem thromboses and profound SNHL affecting the right ear. IgG anticardiolipin antibody was detected without the lupus anticoagulant, and there was a false-positive serologic test for syphilis as is often the case in those with IgG anticardiolipin antibodies. Steroid therapy was commenced and although assays for anticardiolipin antibody became negative as did the serological test for syphilis, there was only a partial recovery of hearing. No anticoagulation was used. This patient would need a second set of antiphospholipid testing to fulfil the criteria for diagnosis of secondary APS, which is the most likely diagnosis in retrospect. Bowman *et al.*¹² studied 30 patients with SLE and found an 8 % incidence of unexplained SNHL. This study, although small suggests a clinically significant link between SLE and SNHL. Antiphospholipid antibodies were unfortunately not tested for in this cohort, but we would strongly suggest that these patients had APS. Naarendorp and Spiera,¹³ similarly described 6 patients with SLE or a lupus like syndrome who presented with sudden SNHL and had elevated levels of anticardiolipin antibodies or the lupus anticoagulant. They contended that SNHL in patients with SLE who have antiphospholipid antibody may be a manifestation of the antiphospholipid antibody syndrome. They recommended antico-

agulation treatment of these patients.

Vyse *et al.*¹⁴ presented a case of a 23 year old primigravida who presented as an emergency at 27 weeks gestation with fulminant pre-eclampsia and bone marrow necrosis. As her mental state improved it became apparent that she was severely deaf and she complained of a loss of balance. There was profound bilateral hearing loss and the calorific response was absent bilaterally. Short term steroid therapy did not result in improvement of the auditory thresholds. IgG anticardiolipin antibody level was grossly elevated and there was a weakly positive lupus anticoagulant. Long term anticoagulation with warfarin was commenced. As expected there was no improvement in hearing thresholds after a 5 year follow up, but she did not have recurrent thrombotic events.

Mouadeb *et al.*¹⁵ investigated 168 patients with unexplained hearing loss. Of the 66 patients with SNHL, 15 had at least one positive anticardiolipin antibody. A much higher number in total, 42 out of the 168 had at least one positive antibody, and of those 14 had at least two positive anticardiolipin antibodies. The time course between testing for anticardiolipin antibodies is unclear, and it seems that many of the patients who were positive did not have a second test 3 months later. Only one patient had an isolated positive lupus anticoagulant. However the authors grouped the patients with Meniere's disease and SNHL together, so they were unable to evaluate the number with SNHL who may fit the diagnostic criteria for APS. Toubi *et al.*¹⁶ addressed the possibility of SNHL and APS. They investigated the association of idiopathic sudden SNHL and various antibodies. In particular they looked at the persistence of aCL and anti- β_2 glycoprotein antibodies over time. In a prospective follow-up study, 51 patients diagnosed with idiopathic sudden SNHL were tested for a range of autoantibodies including the aCL and anti- β_2 glycoprotein. The control population consisted of 35 age-sex matched healthy controls. Positive aCL antibodies were found in 16 patients (31%). After 3 months, aCL persistence was demonstrated in 7 patients, (14%). Of the control population, 2 (6%) were positive for aCL antibodies, which persisted for 3 months in 1 patient (3%). These patients were treated promptly with oral prednisolone, and the authors note no clinical difference was perceived between those with persistently positive aCL antibodies (who we propose fulfil the criteria for APS) and the others studied. The study can be criticised because they did not address the lupus anticoagulant status and therefore other patients with antiphospholipid antibodies may have been missed. In addition, anticoagulation was not contemplated and it would be interesting to discover if there were further thrombotic events in this group of patients. Further studies have looked at the effect of anticoagulation with heparin, both low molecular weight heparin and unfractionated heparin in patients with idiopathic SNHL, in addition to conventional therapies such as intravenous dexamethasone. Yue *et al.*¹⁷ showed an advantage in anticoagulation with low molecular weight heparin in addition to standard therapy, with significant improvement of hearing loss. The results however are difficult to interpret as the anticoagulation was in conjunction with other treatments. They do however, comment on the need for prompt treatment, to maximise reversal of hearing loss. These are one of the few groups that have used anticoagulation in the treatment of SNHL, although as a short term measure. The question of formal anticoagulation for any length of time is rarely addressed, let alone contemplated. This is for a number of reasons, the first, as previously discussed, it is almost impossible to prove that

thrombosis is the cause of SNHL. The possibility of APS as a causative pathology is only now being considered, and still does not seem to be a widespread consideration at acute presentation. Then the issue of long term widely debated, should they be exposed to the side effects of long term anticoagulation, currently warfarin at a high target INR of 3 to 4? In addition, the diagnosis of APS and exclusion of other factors takes some time, and as Yue *et al.* comments on, early anticoagulation is thought to be most beneficial. This could be achieved by initiating anticoagulation with LMWH at presentation whilst further investigations are ongoing, after salient blood tests have been taken, unless there are contraindications. If the diagnosis of APS is made after rigorous exclusion of other causes of SNHL, then formal anticoagulation with an oral anticoagulant should begin. These patients, as any on warfarin, require careful follow up and referral to an anticoagulant clinic. Also the duration of anticoagulation is contentious, if diagnosed with APS, then they are at risk of not only further thrombosis in the cochlear region, but also elsewhere and thus would require long term anticoagulation. Clinical studies are needed to evaluate the timing, efficacy and duration of anticoagulation in this group of patients.

Casoli and Tumati¹⁸ reported the case of a 55 year old female with Cogan's syndrome (non-syphilitic interstitial keratitis, acute SNHL and vestibular symptoms) who presented acutely with vertigo and profound unilateral hearing loss affecting the left ear. IgG, IgM anticardiolipin antibodies and the lupus anticoagulant was detected. There was no improvement in hearing thresholds after an eighteen month follow up. Information is lacking in both of these cases as to whether there was persistence of antiphospholipid antibodies, which is required for a diagnosis of primary APS. Moreover as the anticardiolipin antibody test is derived from the test for syphilis, one might expect false positive tests for anticardiolipin antibody in those with syphilis. However one would not expect a positive lupus anticoagulant in those with syphilis. Susac's syndrome is described as a microangiopathic disorder, presenting in predominantly young women with a triad of encephalopathy, hearing loss and branch retinal vein occlusions. Its pathogenesis is unknown; however there has been some discussion as to its link with thrombosis and APS. Bucciarelli *et al.*¹⁹ presented a case of a 31 year old woman with typical features of Susac's syndrome in whom antiphospholipid antibodies were detected. She had some features of autoimmune disease, with arthralgia, Raynaud's phenomenon and positive ANA, but a negative double stranded DNA. In addition she fulfilled the criteria for APS, with persistent positivity of antiphospholipid antibodies, bilateral retinal thrombosis and sudden SNHL. The authors postulate whether Susac's syndrome is in fact what is described as catastrophic APS, characterised by multiple organ involvement due to thrombotic occlusion of the small vessels.²⁰ Other potential aetiologies include autoimmune, leading to small vessel vasculitis and thus microinfarction.²¹ Differentiation between these aetiologies is difficult without biopsies of the affected area, and current treatment with long term immunosuppressives in addition to anticoagulation does not help in the unravelling of aetiology.

In summary, the two cases we have presented are of patients who presented with sudden SNHL, without any associated stigmata of connective tissue disorders, which we believe were as a manifestation of primary antiphospholipid syndrome. SNHL as is being increasingly recognised in APS, both as a primary event and secondary as

another thrombotic sequel to APS.

Sudden sensorineural hearing loss is a devastating blow to the patient and a diagnostic conundrum for the clinician. Sudden sensorineural hearing loss associated with autoimmune disease and due to a presumed autoimmune vasculitis is reported in a number of connective tissue diseases, including SLE, polyarteritis nodosa, rheumatoid arthritis and relapsing perichondritis.²² However, there may be an alternative pathophysiology in many patients, as a result of microvascular thrombosis as a result of APS. A strong case for investigating these patients for the antiphospholipid syndrome has emerged in the medical literature. Many of the cases previously described describe elevated antiphospholipid antibodies, but few have contemplated the diagnosis of APS. With increasing awareness of the association, it is likely that a strong association will be found, which has immediate prognostic implications for the patient as early anticoagulation may be beneficial in promoting recovery of hearing impairment.

Our patients did not show any improvement in their hearing loss, which may be in part to the delay in the initiation of anticoagulation. Importantly however, they did not develop further thrombosis as they were anticoagulated. There is a serious risk of recurrent thrombosis in patients with previous thrombosis and APS. In the largest retrospective study, 147 patients who had at least one prior thrombotic event were found to have a recurrent thrombosis rate of 69%,⁷ which was in accord with the findings of previous smaller studies.^{23, 24} Life-long anticoagulation, currently with warfarin, as it is the only available oral anticoagulant, is the most effective prophylaxis against further thrombosis. Thus it is currently recommended that once a patient has had a thrombosis associated with APS, long-term warfarin therapy is commenced.²⁵ Thrombotic events are divided into arterial and venous with a target INR of 3.0 to 4.0 for arterial and 2.5 to 3.0 for venous.

We believe that every patient presenting with sudden SNHL should be screened for antiphospholipid antibodies once other causes are excluded (both anticardiolipin antibodies and the lupus anticoagulant must be performed, as only one may be positive) and if confirmed, anticoagulation should begin without delay to prevent further thrombotic events. Long term anticoagulation with warfarin maintaining an INR > 3.0 is required to prevent other arterial thrombotic events.²⁶

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