

# Bilateral sudden sensorineural hearing loss as a presenting feature of systemic lupus erythematosus

## Case report and brief review of other published cases

Sylvain Chawki<sup>a,b,\*</sup>, Jessie Aouizerate, MD<sup>c</sup>, Selim Trad, MD<sup>a,b</sup>, Jacques Prinseau, MD<sup>a,b</sup>, Thomas Hanslik, MD, PhD<sup>a,b,d,e</sup>

### Abstract

**Introduction:** Sudden sensorineural hearing loss is an unusual presenting clinical feature of systemic lupus erythematosus.

**Case report:** We report the case of a young woman who was admitted to hospital for sudden sensorineural hearing loss and hemophagocytic syndrome which was attributed to systemic lupus erythematosus on the basis of specific renal involvement, thrombocytopenia, and consistent autoantibodies. Favorable outcome was obtained on high-dose corticosteroids, and the hearing fully recovered.

**Discussion:** Sudden sensorineural hearing loss in systemic lupus erythematosus is seemingly more frequently associated with severe systemic involvement and antiphospholipid antibodies may be present. Although management remains empirical, the high risk of permanent hearing impairment seems to justify emergency treatment with high-dose corticosteroids. When the clinical and laboratory criteria of antiphospholipid syndrome are met, antiplatelets agents or anticoagulation therapy shall be considered.

**Keywords:** autoimmunity, corticosteroids, sensorineural hearing loss, systemic lupus erythematosus

## 1. Introduction

Sudden sensorineural hearing loss is defined as an acquired hearing deficit of up to 30 dB loss in 3 different frequencies on an audiogram, building up over a few hours to up to 3 days. Five to 20 per 100,000 population are affected, both male and female, typically between 30 and 60 years of age.<sup>[1]</sup> In the majority of cases, hearing loss is unilateral and associated with vestibular symptoms. The pathophysiology is unclear. Viral, genetic, traumatic, or toxic causes have been discussed. Autoimmune or vascular etiology has been put forward in 10% of cases.<sup>[2]</sup>

Sudden sensorineural hearing loss is an unusual presenting clinical feature of systemic lupus erythematosus. We report the

case of a young woman who presented to our hospital for sudden sensorineural hearing loss that was ultimately attributed to systemic lupus erythematosus. We reviewed the medical literature indexed in the Medline database (accessed on December 28, 2015). Our search key words were: “hearing OR sensorineural OR deafness AND lupus,” in all fields, only English and French language articles.

## 2. Case report

A 19-year-old woman was referred to our hospital in December 2006 for a fever, a sudden profound bilateral hearing loss and a malar rash that had appeared 10 days before hospitalization. She had no significant past medical history. Besides hearing loss, physical examination revealed a malar rash, ulcerated stomatitis, enlarged cervical lymph nodes, and subungual hemorrhage. The remainder of the physical examination was normal.

An audiogram showed a hearing threshold of 40 dB in the right ear and 60 dB in the left ear, both in air and bone conduction. Laboratory tests revealed neutropenia (540 neutrophils/ $\mu$ L), thrombocytopenia (125,000/ $\mu$ L), elevated liver enzymes (aspartate aminotransferase 247 IU/L, 8-fold the upper limit of normal range; alanine transaminase 116 IU/L, 3-fold the upper limit of normal range; gamma-glutamyl transferase 166 IU/L, 3-fold the upper limit of normal range and alkaline phosphatase 40 IU/L, normal), hyperferritinemia (10,965  $\mu$ g/L) and an elevated titer of lactate dehydrogenase (989 IU/L, 3-fold the upper limit of normal range), and triglycerides (4.96 g/L, normal range: 0.6–1.9 g/L). Hematuria and leucocyturia were initially detected, with an associated proteinuria (3.13 g/L).

Antinuclear antibodies were positive (titer 1/2560), with antidouble stranded DNA (31 IU) and anti-Sm antibodies. Antinucleosome and anti-SSA antibodies were present as well.

Editor: Carlos Guillen Astete.

The authors have no conflicts of interest to disclose.

<sup>a</sup> Service de Médecine Interne, Hôpital Ambroise Paré, Assistance Publique Hôpitaux de Paris, APHP, Boulogne Billancourt, <sup>b</sup> Université de Versailles Saint Quentin en Yvelines, UVSQ, Versailles, <sup>c</sup> Service de Néphrologie, Hôpital Henri Mondor, Assistance Publique Hôpitaux de Paris, APHP, Créteil, <sup>d</sup> Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Universités, UPMC Univ Paris 06, UMR\_S 1136, <sup>e</sup> INSERM, UMR\_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France.

\* Correspondence: Sylvain Chawki, 20 avenue Corot, Le Vesinet 78110, France (e-mail: sylvain.chawki@gmail.com).

Copyright © 2016 the Author(s). Published by Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

Medicine (2016) 95:36(e4345)

Received: 4 April 2016 / Received in final form: 23 June 2016 / Accepted: 25 June 2016

<http://dx.doi.org/10.1097/MD.0000000000004345>

Coagulation tests disclosed a lupus anticoagulant. Low levels of anticardiolipin antibodies were detected (IgG: 27 µg/L).

Complement was abnormally low with 0.3 g/L C3 (lower limit 0.7 g/L); 0.1 g/L C4 (lower limit 0.1 g/L) and 50% CH50%. Bone marrow aspiration revealed mild hemophagocytosis.

Renal biopsy revealed World Health Organisation class II lupus nephritis with pure mesangial involvement, with IgG, C3, C1q, and IgM deposits on immunofluorescence. There was no alteration of blood vessels (absence of infiltration, necrosis of the vascular wall, or microscopic thromboangiitis), nor proliferation on light microscopy.

Echocardiographic examination was normal, without any valvular abnormality. Cerebral magnetic resonance imaging was normal and displayed no evidence of ischemia.

The patient met the American College of Rheumatology classification criteria for systemic lupus erythematosus. She was treated with high-dose (500 mg) intravenous methylprednisolone for 3 days, and clinically improved within a few days. The hearing completely recovered, as assessed by repeated audiograms. The hemophagocytic syndrome, proteinuria, and hematuria also improved following corticosteroid therapy.

Long-term treatment with prednisone (1 mg/kg/day with gradual decrease), hydroxychloroquine and aspirin was introduced. Six months later, proteinuria and hematuria rebounded and mycophenolate mofetil treatment was introduced. Overall treatment was well tolerated. One year later, clinical examination was normal with a complete remission of systemic lupus erythematosus; mycophenolate mofetil was stopped.

Secondary antiphospholipid syndrome (antiphospholipid syndrome) was excluded on the basis of an uneventful follow-up and the quick fading of anticardiolipin antibodies and lupus anticoagulant that were never detected again over 9 years of follow-up.

A second flare occurred in 2011, with myalgia, arthralgia, fatigue, and hemophagocytic syndrome. This flare was treated by a temporary increase of prednisone dose; no immunosuppressive therapy was necessary. Evolution was unremarkable ever since. When last seen in February 2016, the patient was doing well on 5 mg prednisone and 400 mg hydroxychloroquine daily.

### 3. Discussion

This patient presented with bilateral sudden sensorineural hearing loss in the context of a hemophagocytic syndrome, revealing systemic lupus erythematosus, and raising questions about pathophysiology and treatment. Sudden sensorineural hearing loss should be clearly distinguished from other sensorineural hearing loss in patients with systemic lupus erythematosus. Indeed, systematic audiometric tests have shown that 20% to 55% of systemic lupus erythematosus patients have chronic sensorineural hearing impairment, often asymptomatic.<sup>[3–8]</sup> Thus, the risk of sensorineural hearing loss seems to be much higher in systemic lupus erythematosus patients compared to healthy age-matched controls, with an odds ratio of 20 (95% CI: 2.93–139.6).<sup>[7]</sup> In contrast, sudden sensorineural hearing loss, which is usually a dramatic condition, has been seldom reported in systemic lupus erythematosus patients (Table 1).

Three pathophysiological hypotheses are proposed for sudden sensorineural hearing loss at the beginning of systemic lupus erythematosus manifestations<sup>[9,10]</sup>.

- T-cell autoimmunity: As shown patients with sudden sensorineural hearing loss presented significant proliferation of T

lymphocytes specifically responsive to human inner ear antigens, as well as increased interferon-gamma and other inflammatory intracellular cytokines levels in peripheral blood.<sup>[11–16]</sup>

- Humoral autoimmunity: specific autoantibodies directed against inner-ear antigens have been detected in this context and may be involved in sudden hearing loss.<sup>[17–19]</sup>
- Antiphospholipid syndrome: case reports have highlighted the possible association of anticardiolipin antibodies with sudden sensorineural hearing loss in systemic lupus erythematosus. Antiphospholipid antibodies (i.e., anticardiolipin antibody, lupus anticoagulant, and anti-β2 GP1) are known to be associated with microcirculation thrombosis and histological proof of microinfarctions has been reported in systemic lupus erythematosus patients with sudden sensorineural hearing loss.<sup>[20–22]</sup> High concentrations of antiphospholipid antibodies have been reported in case reports of lupus-associated sudden sensorineural hearing loss, with satisfying clinical response to anticoagulant therapy.<sup>[20,22–26]</sup> Whether the presence of antiphospholipid antibodies in patients presenting sudden sensorineural hearing loss is sufficient to establish a diagnosis of secondary antiphospholipid syndrome in the absence of other symptoms (i.e., thromboembolic or obstetrical complications) remains to be determined.<sup>[20,22,24,25]</sup>

When reviewing the English and French literature in the Medline database, we found 22 documented cases of sudden sensorineural hearing loss in association with systemic lupus erythematosus (Table 1). Patients were between 20 and 50 years old, mostly women (16/22). Hearing loss was unilateral in 14 out of 22 cases. Hearing loss was the first manifestation of systemic lupus erythematosus in four cases. In 11 cases major systemic involvement of systemic lupus erythematosus such as renal, cardiac, or neurological involvement was also reported.

Besides hearing loss, other reported aural symptoms included: middle ear involvement, otitis, and in 9 cases, vestibular symptoms.

When tested, anticardiolipin antibodies, and/or lupus anticoagulant and/or isolated syphilis reaginic antibody proved positive in 11 out of 15 cases. Half of these patients had a past or present medical history of thrombosis. Ten patients had had a brain CT-scan or MRI: among them, 3 had signs of central nervous system ischemia. However, secondary antiphospholipid syndrome was not explicitly considered in several of those cases. Pathological data were available in three cases, showing middle ear lesions such as vasculitis and nonspecific inflammation.

Twelve patients were treated with steroids (0.5–1 mg/kg equivalent prednisone, 1 was treated with 500 mg methylprednisolone on 3 consecutive days), 4 patients were prescribed immunosuppressive therapy with azathioprine or cyclophosphamide, 3 were treated with plasmapheresis and 2 with hydroxychloroquine. Anticoagulation or antiplatelet therapy was prescribed to 4 patients. Clinical outcome was reported for 13 patients: recovery from hearing loss was complete in only 4 patients and partial in 2 other cases. None of the patients treated with anticoagulation or antiplatelet therapy recovered.

A recent publication of a retrospective cohort study from the Taiwan National Health Insurance Research Database reported 27 cases of sudden sensorineural hearing loss associated with systemic lupus erythematosus, but no detail on clinical and biological data was available.<sup>[27]</sup>

We conclude that sudden sensorineural hearing loss can be the presenting clinical feature of systemic lupus erythematosus and may be associated with antiphospholipid antibodies. Although

**Table 1**

**Published case reports of sudden sensorineural hearing loss in patients with systemic lupus erythematosus.**

Refs.	Age/ gender	Time between SLE diagnosis and SSNHL	Unilateral or bilateral SSNHL	Associated SLE symptoms	Laboratory criteria for presence of anti phospholipid*	Treatment	Hearing loss recovery
Hamblin et al. <sup>[28]</sup> , case report	47, F	6 wk	Bilateral	Rash, arthritis, renal insufficiency	ND	Prednisone 40 mg; plasma exchange	ND
Caldarali et al. <sup>[29]</sup> , Case report	51, F	0	Unilateral	Unsteadiness, arthritis	ND	Prednisone (25 mg × 4); oral cyclophosphamide	No
Kobayashi et al. <sup>[30]</sup> , case report	32, F	2 y	Bilateral	Palmar erythema, arthralgia, myalgia, fever, rash, mitral regurgitation, convulsions, lymphadenopathy	Yes	Oral steroids ineffective; plasmapheresis	Yes
Hisashi et al. <sup>[24]</sup> , case report	15, F	2 y	Unilateral	Malar rash, vestibular and cerebellar ataxia, left lateral Horner medullary syndrome, hemiparesis right internuclear ophthalmoplegia	Yes	Prednisone 40 mg	Partial
Wyse et al. <sup>[31]</sup> , case report	23, F	0	Bilateral	Preeclampsia, femoral vein thrombosis, tinnitus, vertigo	Yes	Prednisone; anticoagulation	No
Kataoka et al. <sup>[32]</sup> , case report	40, F	3 mo	Bilateral	Edema, tinnitus	ND	Steroids and cyclophosphamide	Yes
Naarendrop and Spleta <sup>[22]</sup> , 5 case reports	30, F	8 y	Unilateral	Aphasia, hypertension, cerebrovascular accident, malar rash, arthritis, recurrent serositis, abdominal pain, fever	Yes	Antibiotics; methylprednisolone; 2 mg/kg prednisone	Partial
	26, F	4 y	Unilateral	Vertigo, aphasia, hypertension, intermittent vision loss, spontaneous abortions, hyperthyroidism	Yes	ND	ND
	37, M	3 y	Unilateral	Hashimoto thyroiditis, thrombophlebitis, pulmonary embolism, cutaneous lupus, nephritis	Yes	ND	ND
	41, M	0	Unilateral	Malar rash, proteinuria, pericarditis, neuropathy	Yes	ND	ND
	40, M	ND	Unilateral	Chronic sinusitis, asthma, arthralgia, Bell palsy, dizziness, rash	Yes	ND	ND
Paira <sup>[33]</sup> , case report	22, F	ND	Unilateral	Rash, photosensitivity, arthritis, alopecia, Raynaud syndrome	No	ND	ND
Some et al. <sup>[34]</sup> , 2 case reports	22, F	13 y	Unilateral	Arthralgia, renal insufficiency, otitis media	ND	ND	ND
	47, F	26 y	Bilateral	Renal insufficiency	ND	ND	ND
Peeva and Barland <sup>[35]</sup> , 2 case reports	45, F	10 y	Bilateral	Tinnitus, severe aortic insufficiency, photosensitivity, arthralgias, malar rash, fever, pleuropericarditis	Yes	Methylprednisolone 80 mg (3 d)	No
Green and Millie <sup>[21]</sup> , case report	31, F	9 y	Bilateral	Tinnitus, aortic insufficiency, fever, arthralgia, anemia	No	Steroids; hydroxychloroquine	No
	22, M	0	Unilateral	Dizziness, arthralgia, left hemiparesis, scotomas, Crohn colitis, otitis media	Yes	Low molecular weight heparin and warfarin; prednisone; 5-aminosalicylic acid	No
Mora et al. <sup>[36]</sup> , case report	39, M	ND	Unilateral	ND	ND	Enoxaparin	Yes
Compadretti et al. <sup>[20]</sup> , case report	37, F	1 y	Unilateral	Thrombophlebitis	Yes	Betamethasone: 5 mg; hydroxychloroquine: 200 mg; acenocoumarol: 4 mg; glycerol: 500 mL; hydrochlorothiazide: 50 mg	Yes
Fukushima et al. <sup>[37]</sup> , case report	22, F	5 y	Unilateral	Hematologic involvement, arthritis, lupus nephritis	ND	Prednisone; plasmapheresis; azathioprine	ND
Sugiura et al. <sup>[38]</sup> , case report	40, M	7 y	Bilateral	Vestibular syndrome, pleuritis, hemolytic anemia, thrombocytopenia	Yes	Prednisone 60 mg/d; hyperbaric oxygen therapy; glycerol	No
Khalidi et al. <sup>[39]</sup> , case report	33, F	9 y	Unilateral then bilateral	Tinnitus, dizziness, Raynaud phenomenon, pleuritis, polyarthralgia, superior limb venous thrombosis	No	When unilateral symptoms: acyclovir, aspirin; low molecular weight heparin; methylprednisolone 500 mg 3 consecutive days then oral prednisone 5 mg daily; at month 2: bilateral symptoms: oral prednisone 60 mg and azathioprine 200 mg daily	No
Lin et al. <sup>[27]</sup> , population-based, retrospective cohort study	27 cases: 25 F, 2 M; 14: 0-34 y; 13 ≥ 35 y	ND	ND	ND	ND	ND	ND

F = female, M = male, ND = not determined, SLE = systemic lupus erythematosus, SSNHL = sudden sensorineural hearing loss.

\* Syphilis reaginic antibody, anticardiolipin antibody, antiphospholipid antibody, or lupus anticoagulant.

management of such cases remains empirical, the high risk of permanent hearing loss seems to justify emergency treatment with high dose corticosteroids. If the laboratory criteria of antiphospholipid syndrome are present, antiplatelets agents or anticoagulation therapy shall be considered.

Informed oral consent was obtained from the patient.

All data were strictly obtained from the patient's medical file.

## References

- Stachler RJ, Chandrasekhar SS, Archer SM, et al. Clinical practice guideline: sudden hearing loss. *Otolaryngol Head Neck Surg* 2012;146: S1–35.
- Vinceneux P, Couloigner V, Pouchot J, et al. Autoimmune deafness. *Presse Med* 1999;28:1904–10.
- Abbasi M, Yazdi Z, Kazemifar AM, et al. Hearing loss in patients with systemic lupus erythematosus. *Glob J Health Sci* 2013;5:102–6.
- Andonopoulos AP, Naxakis S, Goumas P, et al. Sensorineural hearing disorders in systemic lupus erythematosus. A controlled study. *Clin Exp Rheumatol* 1995;13:137–41.
- Bowman CA, Linthicum FH Jr, Nelson RA, et al. Sensorineural hearing loss associated with systemic lupus erythematosus. *Otolaryngol Head Neck Surg* 1986;94:197–204.
- Kastanioudakis I, Ziavra N, Voulgari PV, et al. Ear involvement in systemic lupus erythematosus patients: a comparative study. *J Laryngol Otol* 2002;116:103–7.
- Roverano S, Cassano G, Paira S, et al. Asymptomatic sensorineural hearing loss in patients with systemic lupus erythematosus. *J Clin Rheumatol* 2006;12:217–20.
- Sperling NM, Tehrani K, Liebling A, et al. Aural symptoms and hearing loss in patients with lupus. *Otolaryngol Head Neck Surg* 1998;118: 762–5.
- Marcucchi R, Alessandrello Liotta A, Cellai AP, et al. Cardiovascular and thrombophilic risk factors for idiopathic sudden sensorineural hearing loss. *J Thromb Haemost* 2005;3:929–34.
- Yehudai D, Shoenfeld Y, Toubi E. The autoimmune characteristics of progressive or sudden sensorineural hearing loss. *Autoimmunity* 2006;39:153–8.
- Harris JP, Woolf NK, Ryan AF. A re-examination of experimental type II collagen autoimmunity: middle and inner ear morphology and function. *Ann Otol Rhinol Laryngol* 1986;95:176–80.
- Hughes GB, Barna BP, Kinney SE, et al. Predictive value of laboratory tests in “autoimmune” inner ear disease: preliminary report. *Laryngoscope* 1986;96:502–5.
- Iwai H, Tomoda K, Sugiura K, et al. T cells infiltrating from the systemic circulation proliferate in the endolymphatic sac. *Ann Otol Rhinol Laryngol* 1999;108:1146–50.
- Lorenz RR, Solares CA, Williams PM, et al. Interferongamma production to inner ear antigens by T cells from patients with autoimmune sensorineural hearing loss. *J Neuroimmunol* 2002;130: 173–8.
- Staecker H, Lefebvre PP. Autoimmune sensorineural hearing loss improved by tumor necrosis factor- $\alpha$  blockade: a case report. *Acta Otolaryngol* 2002;122:684–7.
- Yoo TJ. Etiopathogenesis of Meniere's disease: a hypothesis. *Ann Otol Rhinol Laryngol Suppl* 1984;113:6–12.
- Arnold W, Pfaltz CR. Critical evaluation of the immunofluorescence microscopic test for identification of serum antibodies against human inner ear tissue. *Acta Otolaryngol* 1987;103:373–8.
- Gebbers JO, Altermatt HJ, Arnold W, et al. Binding of serum immunoglobulins to human inner ear tissue in inner ear hearing loss. *HNO* 1987;35:487–91.
- Harris JP. Immunology of the inner ear: immunology of the inner ear: evidence of local antibody production. *Ann Otol Rhinol Laryngol* 1984;93:157–62.
- Compadretti GC, Brandolini C, Tasca I. Sudden SNHL in lupus erythematosus associated with antiphospholipid syndrome. *Ann Otol Rhinol Laryngol* 2005;114:214–8.
- Green L, Miller EB. Sudden sensorineural hearing loss as a first manifestation of systemic lupus erythematosus: association with anticardiolipin antibodies. *Clin Rheumatol* 2001;20:220–2.
- Naarendrop M, Spiera H. Sudden SNHL in patients with SLE and antiphospholipid antibodies. *J Rheumatol* 1998;25:589–92.
- Heller U, Becker EW, Zenner HP, et al. Incidence and clinical relevance of antibodies to phospholipids, serotonin and ganglioside in patients with sudden deafness and progressive inner ear hearing loss. *HNO* 1998;46: 583–6.
- Hisashi K, Komune S, Taira T, et al. Anticardiolipin antibody-induced sudden profound sensorineural hearing loss. *Am J Otol* 1993;14:275–7.
- Mouadeb DA, Ruckenstein MJ. Antiphospholipid inner ear syndrome. *Laryngoscope* 2005;115:879–83.
- Yue WL, Li P, Qi PY, et al. Role of low-molecular-weight heparins in the treatment of sudden hearing loss. *Am J Otolaryngol* 2003;24: 328–33.
- Lin C, Lin SW, Weng SF, et al. Risk of sudden sensorineural hearing loss in patients with systemic lupus erythematosus: a population-based cohort study. *Audiol Neurootol* 2013;18:95–100.
- Hamblin TJ, Mufti GJ, Bracewell A. Severe deafness in systemic lupus erythematosus: its immediate relief by plasma exchange. *Br Med J (Clin Res Ed)* 1982;284:1374.
- Caldarelli DD, Rejowski JE, Corey JP. Sensorineural hearing loss in lupus erythematosus. *Am J Otol* 1986;7:210–3.
- Kobayashi S, Fujishiro N, Sugiyama K. Systemic lupus erythematosus with sensorineural hearing loss and improvement after plasmapheresis using the double filtration method. *Intern Med* 1992;31:778–81.
- Vyse T, Luxon LM, Walport MJ. Audiovestibular manifestations of the antiphospholipid syndrome. *J Laryngol Otol* 1994;108:57–9.
- Kataoka H, Takeda T, Nakatani H, et al. Sensorineural hearing loss of suspected autoimmune etiology: a report of three cases. *Auris Nasus Larynx* 1995;22:53–8.
- Paira SO. Sudden sensorineural hearing loss in patients with systemic lupus erythematosus or lupus-like syndrome and antiphospholipid antibodies. *J Rheumatol* 1998;25:2476–7.
- Sone M, Schachern PA, Paparella MM, et al. Study of systemic lupus erythematosus in temporal bones. *Ann Otol Rhinol Laryngol* 1999; 108:338–44.
- Peeva E, Barland P. Sensorineural hearing loss in conjunction with aortic insufficiency in systemic lupus erythematosus. *Scand J Rheumatol* 2001;30:45–7.
- Mora R, Mora F, Passali FM, et al. Restoration of immune-mediated sensorineural hearing loss with sodium enoxaparin: a case report. *Acta Otolaryngol Suppl* 2004;552:25–8.
- Fukushima N, Fukushima H, Cureoglu S, et al. Hearing loss associated with systemic lupus erythematosus: temporal bone histopathology. *Otol Neurotol* 2006;27:127–8.
- Sugiura M, Naganawa S, Teranishi M, et al. Inner ear hemorrhage in systemic lupus erythematosus. *Laryngoscope* 2006;116:826–8.
- Khalidi NA, Rebello R, Robertson DD. Sensorineural hearing loss in systemic lupus erythematosus: case report and literature review. *J Laryngol Otol* 2008;122:1371–6.