EXTENDED REPORT

The HELLP syndrome in the antiphospholipid syndrome: retrospective study of 16 cases in 15 women

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Ann Rheum Dis 2005;**64**:273–278. doi: 10.1136/ard.2003.019000

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Accepted 6 July 2004

Objective: To study the characteristics of the haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome in the antiphospholipid syndrome (APS) and its influence on the subsequent pregnancies.
Methods: This was a retrospective analysis of 16 episodes of HELLP complicating APS in 15 women.
Results: HELLP was complete in 10 cases and partial in six. It occurred during the second trimester in seven cases (the earliest at 18 weeks' gestation), the third trimester in seven cases, and the day following delivery in two cases. Pre-eclampsia was present in six cases and eclampsia in five. Outcome of pregnancies was: live birth (n = 8), stillbirth (n = 2) and fetal death (n = 6). APS was primary in nine women and secondary to systemic lupus erythematosus (SLE) in six. HELLP revealed primary APS in six cases. Seven women were not treated. Low dose aspirin was empirically prescribed in one woman whose APS had been undiagnosed despite a history of two fetal deaths. In the other women, therapy consisted of aspirin (n = 8), low molecular weight heparin with a dose varying between 3000 and 12 000 U daily (n = 5), and high dose immunoglobulin every 4 weeks (n = 2), hydroxychloroquine (n = 4), and prednisone (n = 6). Six women had seven subsequent pregnancies, 3–6 years after the complicated pregnancy. HELLP recurred at 33 weeks' gestation in one woman with SLE treated with prednisone, hydroxychloroquine, aspirin, and enoxaparin, and pregnancy ended in live birth. One woman became pregnant after in vitro fertilisation and embryo transfer, but pregnancy ended in fetal death despite prednisone, hydroxychloroquine, and enoxaparin. Four women had five uneventful pregnancies with 100 mg daily aspirin and heparin.
Conclusions: APS may be revealed by HELLP. In APS, HELLP is associated with pre-eclampsia/eclampsia in most cases and seems to occur earlier than in the general population. Heparin plus aspirin may prevent obstetric complications in the subsequent pregnancies.

Incidence of haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome in pregnancy has been estimated at 0.01–0.2% in the general population, and at 10–12% in pregnancies complicated with pre-eclampsia/eclampsia. During a 15 year period in a tertiary care centre serving a population area with 40 000 deliveries per year, 442 HELLP syndromes were observed.[1] During the same period, 2331 pregnancies were complicated by pre-eclampsia or eclampsia. Reports of HELLP syndrome complicating APS are scarce. We report a series of 16 episodes of HELLP syndrome complicating primary or secondary APS in 15 women, and describe its characteristics and its influence on the subsequent pregnancies.

PATIENTS AND DEFINITIONS

We retrospectively reviewed the data of 16 pregnancies in 15 women with APS complicated with HELLP syndrome. Diagnosis of APS was based on the international criteria.[2] Lupus anticoagulant (LA) was usually detected by activated partial thromboplastin time (PTT), diluted thromboplastin time, or kaolin clotting time. Abnormal coagulation times were confirmed by mixing patient and control plasma on a 1:1 ratio in order to exclude clotting factor deficiencies. IgG and IgM anticardiolipin (aCL) antibodies were measured by ELISA. IgG and IgM rates were reported as negative if <15 U/ml, as low positive at 16–25 U/ml, as medium positive at 26–80 U/ml and as high positive if >80 U/ml.

Diagnosis of HELLP was based on the presence of haemolysis (anaemia with characteristic peripheral blood smear), lactate dehydrogenase (LDH) over the upper normal value or total bilirubin >12 mg/l, elevated alanine aminotransferase (AAT) >twofold the upper normal value, and nadir platelet count below 125 000/mm^3. Complete HELLP was defined by presence of all criteria, and partial HELLP by the presence of two criteria.[3] Diagnosis of systemic lupus erythematosus (SLE) was based on the revised ACR criteria.[4] The other definitions were: (*a*) embryonic loss (spontaneous termination of pregnancy prior to 10 weeks' gestation)); (*b*) fetal death (according to Branch's definition,[5] death of a fetus demonstrated to be alive at or beyond 10 weeks' gestation); (*c*) premature birth (termination of pregnancy with a live birth below 37 weeks' gestation); (*d*) full term birth (termination of pregnancy with a live birth between 38 and 40 weeks); (*e*) intrauterine growth retardation (IUGR) (birth weight below the 10th centile for the stated gestation); (*f*) hypertension (diastolic pressure >90 mm Hg); (*g*) pre-eclampsia (hypertension complicated with proteinuria ⩾0.5 g/24 hours or oedema or both); and (*h*) eclampsia (pre-eclampsia complicated with seizures or fitting.

RESULTS

At the first episode of HELLP, the mean age was 30 years (range 22–37). Seven women were nulliparous. Pregnancy was the second in four women, the third in two women, the fourth for one woman, and the tenth for one other woman.

Abbreviations: AAT, alanine aminotransferase; aCL, anticardiolipin; APS, antiphospholipid syndrome, APTT, activated partial thromboplastin time; HELLP, haemolysis, elevated liver enzymes, low platelets; IUGR, intrauterine growth retardation; LA, lupus anticoagulant; LDH, lactate dehydrogenase; LMWH, low molecular weight heparin; SLE, systemic lupus erythematosus

Eight women had been previously pregnant with a total of 15 pregnancies. Two women had had a total of four normal pregnancies before SLE/APS onset. Hence, 11 pregnancies were complicated with fetal death (n = 9), embryonic loss (n = 1), and live birth at full term of a growth retarded baby (n = 1).

APS was primary in nine women and secondary to SLE in six. Primary APS was known in only one of the women, who had a history of repeated fetal loss and stroke; 2/8 women with unknown primary APS had been undiagnosed, although there was a suggestive history. One woman had a history of two successive fetal deaths, and another woman had a false positive syphilis test. Hence, HELLP revealed primary APS in six cases.

Of the six women with SLE, APS was known in four, who had a history of thrombophlebitis with fetal death (n = 2), repeated fetal deaths (n = 1), and ischaemic cerebral stroke with embryonic loss (n = 1). Two women with SLE had prior asymptomatic aCL until onset of HELLP complicated with fetal death (n = 2).

Seven women whose pregnancy was complicated by HELLP had not been previously treated. Low dose aspirin was empirically prescribed in one woman whose APS had been undiagnosed despite a history of two fetal deaths. Three women were treated with aspirin plus low molecular weight heparin (LMWH) with a dose varying between 3000 and 8000 U daily. Two women with prior complicated pregnancy under aspirin and LMWH were treated with LMWH 12 000 U daily, aspirin 100 mg/day, and high dose immunoglobulin 80 g twice daily every 4 weeks. One woman with primary ASP complicated with autoimmune thrombocytopenia was treated with hydroxychloroquine and 5 mg daily prednisone. All women with SLE, except one woman who was not treated, received prednisone with a dose ranging between 5 and 30 mg/day and aspirin 100 mg/day. Hydroxychloroquine was maintained in three women and withdrawn in two others.

HELLP was complete in 10 cases and partial in six. It occurred during the second trimester in seven cases (the earliest at 18 weeks' gestation), the third trimester in seven, and in two cases, it appeared the day following delivery (fig 1). The main characteristics of HELLP are summarised in table 1.

Outcome of pregnancy was: live birth of a eutrophic (n = 3) or a hypotrophic baby (n = 5), at full (n = 2) or premature term (n = 6), stillbirth (n = 3), and fetal death (n = 5). Table 2 summarises the pregnancy outcome according to the date of HELLP onset. Fetal death and stillbirth were observed only in HELLP occurring during the second trimester. Apart from two women (one who developed HELLP at 36 weeks' gestation and another in the post-partum period), all deliveries were made by caesarean section. The main paediatric complications were observed in a 25 week old premature newborn, who developed a severe membrane hyaline disease evolving towards broncho-pulmonary dysplasia. The child needed mechanical ventilation for 43 days, and this period was complicated by multiple infections, metabolic anomalies, enterocolitis, neutropenia, and thrombocytopenia. Craniosynostosis needed surgical repair 1 year later. At the present time, this child continues to have retarded stature.

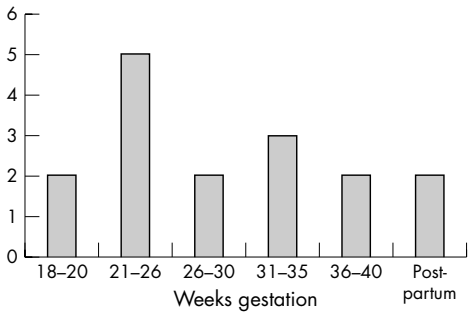

Figure 1 Date of HELLP onset in APS.

Table 1 Main characteristics of HELLP complicating the APS and comparison with series of HELLP in referral obstetric centres

	APS present series(n = 16)	Martin[6] Class3–Class1	Sibai[1]	Audibert[3]
HELLP onset:				
Ante-partum	14 (87.5%)	–	70%	–
Post-partum	2 (12.5%)	–	30%	–
Elevated aminotransferase	15 (94%)	100%	100%	90%
Thrombocytopenia	15 (94%)	100%	100%	75%
Hypertension	11 (69%)	70–90%	65%	–
Proteinuria >0.5g/day	11 (69%)	80–90%	100%	–
Haemolysis	10 (62.5%)	100%	100%	51%
Abdominal pain	7 (44%)	16–50%	100%	73%
Eclampsia	5 (31%)	4–13%	–	8%
Ascites	3 (19%)	–	32%	–
Seizures	3 (19%)	–	–	–
Coagulopathy	2 (12.5%)	8–32%	21%	11%

Pre-eclampsia was present in six cases and eclampsia in five. Among these 11 cases, outcome of pregnancy was: fetal deaths (n = 4), stillbirth (n = 3), and delivery of hypotrophic (n = 3) or eutrophic (n = 1) liveborns. One woman had an abrupted placenta. No hepatic infarction was observed.

Maternal therapy included anti-hypertensive therapy, transfusion, and other supportive care, including mechanical ventilation for 4−14 days in three women. Dexamethasone or betamethasone were prescribed in order to accelerate fetal maturation. No patient needed plasma exchanges, and none of the women died. One woman remained hypertensive and needed permanent medication.

Six women had seven subsequent pregnancies, 3–6 years after the pregnancy complicated by HELLP (table 3). HELLP recurred at 33 weeks' gestation in one woman (patient 1) with SLE treated with prednisone, hydroxychloroquine, aspirin, and enoxaparin. Caesarean section delivered a 2100 g live born child, and a rapid remission of laboratory abnormalities followed. One woman became pregnant after in vitro fertilisation and embryo transfer but pregnancy ended in fetal death despite prednisone, hydroxychloroquine, and enoxaparin (patient 2). Four women had five uneventful pregnancies with 100 mg daily aspirin and heparin (patients 3–6).

Table 2 Pregnancy outcome in our series according to the date of HELLP onset

	Second trimester (n = 7)	Third trimester (n = 7)	Post-partum period(n = 2)
Fetal death	4	0	0
Stillbirth	2	0	0
Livebirth	1	7	2
Hypotrophy	1	4	2
Caesarean section	2	6	1

Table 3 Characteristics of six women with APS complicated with HELLP who had seven subsequent pregnancies

Patient ID/Age	Known disease	Prior events	Therapy	Outcome
Case 1				
23 years	SLE/APS	Normal pregnancy before SLE onset, 2 fetal deaths after		
25 years		HELLP at 31 weeks	CT 10 mg/day, HC, ASP, LMWH 8 000U/day	Live birth
28 years			CT 10 mg/day, HC, ASP, LMWH 8000U/day	HELLP at 33 weeks. Live birth
Case 2				
35 years	SLE/APS	IVFET HELLP at 18 weeks	LMWH 3 000 U/day	Fetal death
37 years		IVFET	CT 10 mg/day, HC, LWMH 8000 U/day	Embryonic loss 15 days after transfer
Case 3				
23 years	SLE/APS	HELLP at 23 weeks	No	Fetal death
25 years			CT 10 mg/day, HC, ASP, LMWH 4000 U/day	Live birth at 37 weeks
27 years			CT 10 mg/day, HC, ASP, LMWH 4000 U/day	Live birth at 38 weeks
Case 4				
28 years	No	HELLP at 40 weeks with eclampsia. Thrombophlebitis in post-partum period	No	Live birth. Diagnosis of primary APS
32 years	APS		LWMH 14 000 U/day, ASP	Live birth at 38 weeks
Case 5				
32 years	False positive syphilis serology	HELLP at 30 weeks	No	Live birth but death at 5 months of life. Diagnosis of primary APS
	APS	With eclampsia	LWMH 6 000 U/day, ASP	Live birth at 39 weeks
Case 6				
29 years	1 embryonic loss	HELPP at 37 weeks	No	Live birth
32 years		With eclampsia	APS, Calcium heparin 0.6 ml×2	Live birth at 39 weeks

CT, prednisone; HC, hydroxychloroquine 400 mg/day; LMWH, low molecular weight heparin; ASP, aspirin 100 mg/day; IVFET, in vitro fertilisation with embryo transfer.

At the present time, all women are doing well, with a mean follow up of 7 years. No vascular complication was observed. All the women with APS characterised only by obstetric complications are being treated with 100 mg daily aspirin, except one woman who has had no therapy. All women with APS with both history of vascular occlusion and obstetric complication are treated with oral anticoagulation. All six women with SLE are in remission with prednisone (n = 4, with a dose ranging between 2 and 12.5 mg daily) and/or hydroxychloroquine (n = 6).

DISCUSSION

HELLP syndrome was described in 1982 by Westein as the association of microangiopathic haemolytic anaemia, hepatitis, and thrombocytopenia in a particular group of pre-eclamptic women, but there are no consensus criteria for its diagnosis. In Martin's study,[6] HELLP was diagnosed on the basis of thrombocytopenia $\leqslant$ 150 000/μL), hepatic dysfunction (increased AAT or alanine aminotransferase $\geqslant$40 U/l), and haemolysis (increased LDH $\geqslant$600 U/l, progressive anaemia). Martin also classified HELLP on the basis of the platelet count nadir: class 1 when platelet nadir is $\leqslant$50 000/mm^3, class 2 at 50 000–100 000/mm^3, and class 3 at 100 000–150 000/mm^3. Incidence of eclampsia, epigastric pain, major maternal morbidity, and stillbirth increases as HELLP worsens from class 3 to class 1. In Sibai's study,[1] HELLP was diagnosed when pre-eclampsia was associated with all the following laboratory abnormalities: characteristic peripheral blood smear, LDH>600 U/l (or total bilirubin >12 mg/l), AAT>70 U/l, and platelet count <100 000/mm^3. Audibert[3] defined complete HELLP by the presence of all three of the following criteria: haemolysis (characteristic peripheral blood smear and LDH $\geqslant$600 U/l), AAT$\geqslant$70 U/l, and platelet count <100 000/μL. Partial HELLP was defined by the presence of one or two features of HELLP. Patients with complete HELLP had a higher risk of caesarean section, disseminated intravascular coagulation, and need for transfusion than those with partial HELLP or pre-eclampsia.

The risk of HELLP is probably increased in APS. However, its incidence is difficult to estimate from the literature, especially after the recent changes in APS criteria.[2] The number of HELLP complicating APS cases reported in the English literature is <30. A recent literature review found 10 cases,[7] to which should be added their two cases, seven cases published in 2002–2003,[19–22] six earlier cases,[8 9 13 15 16] and a few cases cited in APS pregnancies series.[23–25] Our series of 75 pregnancies in primary or secondary APS[23] included seven women (also included in this study), who had eight episodes of HELLP. Backos[24] reported two HELLP in a series of 150 APS pregnancies. In a placebo controlled study of intravenous immunoglobulin treatment for APS, Branch observed that 6/16 women developed severe pre-eclampsia and/or HELLP.[25] However, most series of APS pregnancies did not report any case of HELLP,[26–36] although the rate of pre-eclampsia varied between 0 and 51%.

The high rate of HELLP observed in our series (10.6%), contrasts with 0.66% in that of Backos;[24] this can be explained by different recruitment criteria, as Backos included only primary APS without history of thrombophlebitis. On the other hand, the frequency of APS in HELLP is not well known. In our series, HELLP revealed APS in 8/15 cases. HELLP also revealed APS in half of the 24 well described cases in the literature (table 4). A systematic screening of thrombophilia in 93 women with a history of severe pre-eclampsia/HELLP found antiphospholipid antibodies in 66% of the cases.[37] Although the cut off level was low (5 U/ml), the difference in prevalence compared with controls was significant ($p<0.001$). In France, a systematic search for antiphospholipid antibodies in 68 consecutive cases of complete HELLP among 15 000 deliveries, displayed nine

Table 4 Literature review of 24 well described cases of HELLP syndrome complicating APS

Authors, case, age, age of HELLP onset	History and previous diagnosis	Antiphospholipid antibodies/Therapy	Fetal outcome	Mother's outcome
Kinoshita[8]				
Case 1				
25 years, 23 weeks	No diagnosis	LA, aCL/No therapy	Fetal death	Liver infarction
29 years, 29 weeks	HELLP, 1 fetal death	No therapy	Live birth	Pre-eclampsia. Liver infarction. 3rd pregnancy with live birth with CT
Hochfeld[9]				
Case 2				
37 years, 21 weeks	Superficial phlebitis, 3 fetal losses, APS	LA, aCL/ASP	Fetal death	Fatal catastrophic syndrome
Ornstein[10]				
Case 3				
29 years, 31 weeks	No diagnosis	aCL/No therapy	Live birth	
Case 4				
33 years, 18 weeks	Thrombophlebitis, SLE/APS	LA, aCL/ASP, heparin	Live birth	Skin necrosis
Ilbery[11]				
Case 5				
33 years, 37 weeks	No diagnosis	LA, aCL/No therapy	Live birth	Skin necrosis. Adrenal and liver infarction
Alsulyman[12]				
Case 6				
25 years, 17 weeks	Thrombophlebitis, APS	LA/Heparin	Fetal death	
Case 7				
21 years, 17 weeks	No diagnosis	LA/No therapy	Fetal death	
Case 8				
24 years, 19 weeks	No diagnosis	LA, aCL/No therapy	Fetal death	Pre-eclampsia. Liver infarction
Segal[13]				
Case 9				
27 years, 34 weeks	No diagnosis	aCL	Live birth	Pre-eclampsia. Budd-Chiari syndrome
Amant[14]				
Case 10				
30 years, 29 weeks	Thrombophlebitis	LA/ASP, heparin	Live birth	Liver infarction
Case 11				
29 years, 35 weeks	1 fetal loss, no diagnosis	aCL/ASP	Live birth	Liver infarction
Nagayama[15]				
Case 12				
28 years, 16 weeks	1 embryonic loss, no diagnosis	aCL/No therapy	Induced abortion	
Neuwelt[16]				
Case 13				
31 years, 7 months	2 fetal deaths, pre-eclampsia, no diagnosis	LA, aCL/No therapy	Neonatal death	Pre-eclampsia. Catastrophic syndrome 31 years later
Mc Mahon[17]				
Case 14				
26 years, 18 weeks	No diagnosis	LA/No therapy	Fetal death	
Fehr[18]				
Case 15				
30 years, 15 weeks	Thrombophlebitis, stroke, SLE	aCL/ASP	Fetal death	Liver infarction
Sinha[19]				
Case 16				
26 years, 25 weeks	None, SLE	aCL/ASP, heparin	Neonatal death	Pre-eclampsia. Fatal catastrophic syndrome
Pauzner[20]				
Case 17				
33 years, 25 weeks	13 spontaneous abortions, popliteal artery and femoral vein thrombosis, APS	LA, aCL/ASP, heparin	Neonatal death	Pre-eclampsia. Liver infarction
Case 18				
37 years, 17 weeks	1 fetal death, liver infarction, APS	LA, aCL/ASP, heparin	Fetal death	Liver infarction
Case 19				
31 years, 17 weeks	3 fetal deaths, APS	LA, aCL ASP, heparin	Induced abortion	Liver infarction
Case 20				
28 years, 8 weeks	3 fetal deaths, thrombophlebitis, APS	LA, aCL/Heparin	Induced abortion	Liver infarction
Haram[21]				
Case 21				
28 years, 18 weeks	Recurrent thrombophlebitis and fetal losses, APS	LA, aCL/ASP, heparin	Induced abortion	
Roberts[22] Case 22				
30 years, 36 weeks	Fetal death, SLE/APS	LA ASP, heparin	Live birth	Pre-eclampsia. Renal microangiopathy. Cerebral haemorrhage
Queyrel[7]				
Case 23				
25 years, 27 weeks	2 fetal deaths, no diagnosis	LA, aCL, No therapy	Live birth	
Case 24				
32 years, 24 weeks	Thrombophlebitis, no diagnosis	LA, No therapy	Induced abortion	Skin necrosis

CT, prednisone; ASP, low dose aspirin.

positive cases. Seven of these were subsequently tested, and only two were diagnosed as primary APS. Hence, APS prevalence in HELPP is estimated at 3−6%.[7]

In our series, HELLP occurred in 44% of the cases during the second trimester and 12.5% at 18–20 weeks. In a literature review of the 24 well described cases of HELLP complicating APS, HELLP occurred also before 27 weeks' gestation in 16 cases (table 1). Early HELLP onset was described in association with APS as early as at 8 weeks' gestation.[20] In Sibai's study,[1] HELLP occurred in 2.5% of the cases at 17–20 weeks, in 71% of the cases at 27–36 weeks, in 18% at 37–42 weeks, and in 30% during the post-partum period.

HELLP appears more severe in APS than in the general population. In our series, more than two thirds of the cases were associated with pre-eclampsia/eclampsia, and two cases were complicated by microangiopathic coagulopathy. Six of the 24 cases of well described HELLP complicating APS were associated with pre-eclampsia (table 1). We did not observe any case of liver infarction, which Pauzner found to be almost always associated with APS.[20] In one case of HELLP in APS, hepatic involvement was due to complete thrombosis of hepatic veins.[13]

HELLP may also be part of the catastrophic syndrome, similarly to Hochfeld's case.[9] Catastrophic APS is an acute and devastating disseminated coagulopathy defined by the clinical involvement of at least three different organ systems over a short period.[38] One fatal case of HELLP with catastrophic syndrome was characterised by bone marrow necrosis.[19]

In our study, all HELLP resolved with delivery and/or supportive care. There was no case of maternal death, similarly to the series of Backos and Branch.[24 25] In the general population, HELLP syndrome mortality is about 1%.[1] In the literature, besides the catastrophic syndrome, some cases of HELLP complicating APS were refractory to corticosteroids and anticoagulation. Treatment of refractory HELLP is not standardised. Remission may be observed after plasma exchanges.[22] Dexamethasone appeared to be more effective than betamethasone.[39] Combination of plasma exchanges with fresh frozen plasma has been advocated.[1] In our studies, six women had seven subsequent pregnancies treated with aspirin plus LMWH; one pregnancy was complicated by HELLP recurrence but resulted in live birth, another one with embryonic loss. The other pregnancies ended in live birth. There are no data concerning the risk of HELLP recurrence in APS. Of four cases of HELLP complicating APS, Pauzner reported one recurrence of liver infarction despite aspirin and 60 mg daily enoxaparin.[20] In the general population, HELLP recurred in 5% of subsequent pregnancies in women with a history of HELLP at $\leqslant$30 weeks' gestation.[40]

In conclusion, APS may be revealed by the HELLP syndrome. Search for antiphospholipid antibodies is mandatory in such circumstances. In APS, HELLP is associated with pre-eclampsia/eclampsia in most cases, and seems to occur earlier than in the general population. Heparin plus aspirin may prevent obstetric complications in the subsequent pregnancies.

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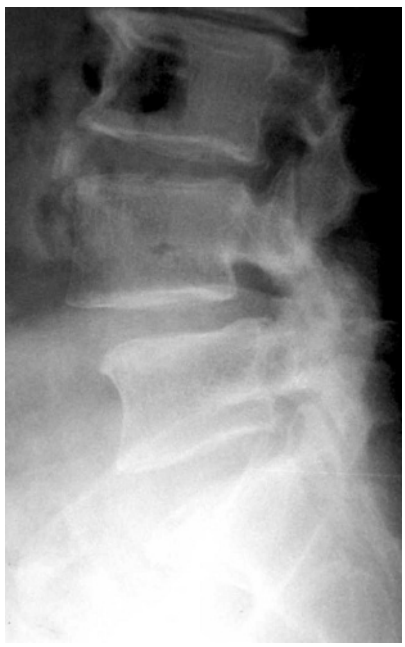
ECHO

Vertebral slippage causes taxi drivers' back pain



ASL in a male taxi driver: lateral view of grade 1 spondylolisthesis of L4 on L5.

A cross sectional study linking acquired lumbar spondylolisthesis with taxi drivers may ultimately lead to preventive measures against this important cause of disabling back pain. It is the first analytical study to show a link with this occupation.

Not only was taxi driving significantly associated with acquired spondylolisthesis (ASL), those who had worked as taxi drivers longest had the highest risk. Drivers with 15 years' service or more had over three times the risk than drivers with up to 5 years' service, and drivers with 6–15 years' service had almost twice the risk, after adjustment for confounding factors. Age, overweight or obesity, and frequent strenuous exercise were also associated with the condition.

Baseline data from the taxi drivers health study, part of a Taipei city government backed programme to monitor taxi drivers' health, were used for the regression analyses. The data covered a sample cohort of 1242 registered taxi drivers in the city who had been operating for at least one year during the first five months of 2000. ASL was diagnosed as non-lytic spondylolisthesis above L5 from lumbosacral *x* ray films; demographic data and data about the job and health behaviours were taken from standard self administered questionnaires.

Our knowledge about ASL comes mostly from descriptive work, but identifying the environmental and work factors on which to base preventive measures needs more population based studies. The next step will be to test these results in prospective studies and then to pinpoint work exposures carrying a risk for the condition.

▲ Chen J-C, *et al*. *Occupational and Environmental Medicine* 2004;**61**:992–998.

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