The pathophysiology of alveolar osteonecrosis of the jaw: Anticardiolipin antibodies, thrombophilia, and hypofibrinolysis

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We studied 55 patients (50 women, 5 men) with severe facial pain and biopsy-proven neuralgia-inducing cavitational osteonecrosis (NICO) of the alveolar bone of the jaws. Our aim was to assess the pathophysiologic contributions to NICO of anticardiolipin antibodies (aCLA), thrombophilia (increased tendency to intravascular thrombi), and hypofibrinolysis (reduced ability to lyse thrombi). Of the 55 patients, 43 (78%) had one or more tests positive for thrombophilia or hypofibrinolysis (or both), and only 12 (22%) were normal. Eighteen of 55 (33%) patients had high aCLA (>2 SD above mean value for control subjects); immunoglobulin G (IgG) (p = 0.01) and immunoglobulin A (IgA)(p = 0.001) levels were higher in patients than in controls. The distribution of elevated aCLA immunoglobulin classes among patients was as follows: IgG alone, 5 (9%); IgA alone, 7 (13%); and IgM alone, 3 (5%). Three patients (5%) had high levels of both IgG and IgA aCLA. Other defects of the thrombotic or fibrinolytic systems in the 55 patients included high lipoprotein(a) in 36% (vs 20% in control subjects (p = 0.03)), low stimulated tissue plasminogen activator activity (tPA-Fx) in 22% (vs 7% in control subjects (p = 0.08)), high plasminogen activator inhibitor activity (PAI-Fx) in 18% (vs 8% in control subjects (p = 0.03)), resistance to activated protein C in 16% (vs 0% in control subjects (p = 0.007)), low antigenic protein C in 4% (vs 0% in control subjects (p > 0.2)), and low antigenic protein S in 4% (vs 0% in control subjects (p > 0.2)). Anticardiolipin antibodies and other defects of the thrombotic and fibrinolytic systems appear to be common, potentially reversible pathogenetic risk factors associated with osteonecrosis of the jaw. (J LAB CLIN MED 1996;127:481-8)

Abbreviations: aCLA = anticardiolipin antibody; APCR = activated protein C resistance; ELISA = enzyme-linked immunosorbent assay; IgG = immunoglobulin G; Lp(a) = lipoprotein(a); NICO = neuralgia-inducing cavitational osteonecrosis of the jaw; PAI-Fx = plasminogen activator inhibitor activity (the major inhibitor of fibrinolysis); tPA-Fx = stimulated tissue plasminogen activator activity (the major stimulator of fibrinolysis)

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Neuralgia-inducing cavitational osteonecrosis of the jaw is a syndrome of chronic neuralgia-like facial pain associated with intraosseous cavity formation and long-standing cancellous bone necrosis of the jaws with minimal regenerative capabilities.[1,2] Although no pathophysiologic causes had been recognized before the cur-

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rent study was performed, the lesion appears sufficiently unique, based on microscopic anatomy and pathology, to recommend this syndrome as a distinct entity.[1,2] It has been speculated that the osteonecrosis may result from persistent thrombosis or hypofibrinolysis, with occlusion of intramedullary veins and sinusoids responsible for the outflow of blood from the internal aspects of the jaws.[1-5] This could, speculatively, progress to increased intramedullary pressure, hypoxia, and bone cell death.[1-3]

Because aCLAs have been associated with thrombophilia[6-9] and with avascular necrosis of bone,[10-15] the specific aim of the current study was to evaluate the prevalence of aCLA (IgG, IgA, and IgM classes) in patients diagnosed with NICO. The association of aCLA with other concurrent thrombophilic or hypofibrinolytic plasma defects[16-19] was also evaluated.

METHODS

Patients. The 55 patients (50 women, 5 men) were referred from the practices of three endodontic surgeons and one oral/maxillofacial surgeon who have a special interest in the diagnosis and management of "idiopathic" facial pain. All patients had biopsy samples interpreted by an oral pathologist with advanced training in bone pathology (J.E.B.), with the histopathology being consistent with changes previously reported in NICO.[1,2] All 55 patients had failed to respond to conventional medical and dental treatments including endodontic therapy, dental extraction, and surgical curettage of the diseased bone. They were studied in the sequence of their referral, without selection bias of age, sex, and duration or severity of osteonecrosis.

Control subjects. tPA-Fx levels in patients were compared with those in 29 normolipidemic control subjects who were sampled during our recent studies of hypofibrinolysis in patients with osteonecrosis.[16] PAI-Fx levels in patients were compared with those in 175 recently reported control subjects in our study of ischemic stroke.[17] Measures of resistance to activated protein C in patients were compared with those in 40 normal healthy hospital personnel. Antigenic protein C, S, and Lp(a) levels were in patients were compared, respectively, with those in 36 and 90 healthy subjects (spouses and unrelated family members) sampled in family studies of Legg-Perthes disease.[18,19] aCLA levels of immunoglobulin classes IgG, IgA, and IgM in patients were compared with levels in 60 normal healthy hospital personnel (33 men and 27 women) between the ages of 20 and 50 years. Although it was not possible to measure all of the tests of coagulation in a single group of adult control subjects, these coagulation tests are not affected by age (in adults) and sex,[5,16-19] and the patient-control comparisons should be valid.

Study protocol, laboratory methods. The study followed an Institutional Research Committee–approved protocol, with signed informed consent. Blood was drawn after a 12-hour fast and seated for 5 to 10 minutes. Because tPA-Fx and PAI-Fx have substantial diurnal variations, blood was drawn from the antecubital vein in a 2-hour "window" between the hours of 8 and 10 AM to minimize circadian influence on fibrinolytic activity.[5,16-19] After the first 3 ml was discarded, blood was collected in 5 ml of 0.13 mol/L (3.8%) sodium citrate–treated Vacutainer tubes and immediately placed in wet ice for transport to the laboratory. For measures of baseline tPA levels, blood was collected in 5 ml Stabilyte tubes (American Diagnostica, Greenwich, Conn.) that contained an acidified citrate anticoagulant solution that preserves the level of tPA activity. With the subject remaining seated during a standard stimulus, 10 minutes of venous occlusion at 100 mm Hg with a blood pressure cuff, citrated blood was again collected (as above) for measurement of tPA-Fx as previously described.[5,16-19] Within 60 minutes of collection, the blood samples were centrifuged at 2000 *g* for 20 minutes at 4° C. Platelet-poor plasma was snap frozen and stored at −70° C until processed.

Functional tPA-Fx and functional PAI-Fx were quantitated by the chromogenic assay kit Spectrolyse (pL) PAI (Biopool, American Diagnostica).[5,16-19] Protein C antigen (Asserachrom Protein C; American Bioproducts, Parsippany, N.J.) and protein S antigen (Asserachrom Protein S; American Bioproducts) in plasma were quantitatively determined by ELISA.[18,19] APCR was measured functionally by clotting technique with the COATEST APC Resistance assay (Chromogenix AB, Molnal, Sweden). The result was expressed as the ratio of the clotting time of plasma with the addition of APC to the clotting time without APC. Lp(a) was measured by immunoprecipitin analysis[5]; levels >25 mg/dl were identified as high. aCLAs were semiquantitatively determined by a solid-phase ELISA for IgG and IgM antibodies (Reaads Anticardiolipin microwell test kit; Reaads Medical Products Inc., Westminster, Colo.). Anticardiolipin IgA was determined by the Reaads IgA anticardiolipin ELISA test kit. Results were read as optical density (absorbance), and antibody levels were expressed in IgG, IgM, or IgA units. Levels greater than 2 SD of the mean of the 60 control subjects were considered high (Fig. 1). The lupus anticoagulant was not measured.[20]

Study protocol, clinical and dental evaluation. At the initial visit, a detailed medical and family history was systematically obtained that included questions focusing on known risk factors for secondary osteonecrosis such as long-term corticosteroid use, sickle cell trait, alcoholism, trauma, systemic lupus erythematosus, and dysbaric exposure.[16,19,21,22] The patients' histories of facial pain and their medical and surgical therapies for facial and jaw pain were systematically recorded. In addition, patients' histories of dental surgery including endodontic therapy, extractions, bone biopsies, and treatment for odontogenic or osseous infections were provided by the referring oral and endodontic surgeons.

Statistical methods. The distribution of the data was analyzed by the Shapiro-Wilk test.[23] The data were pre-

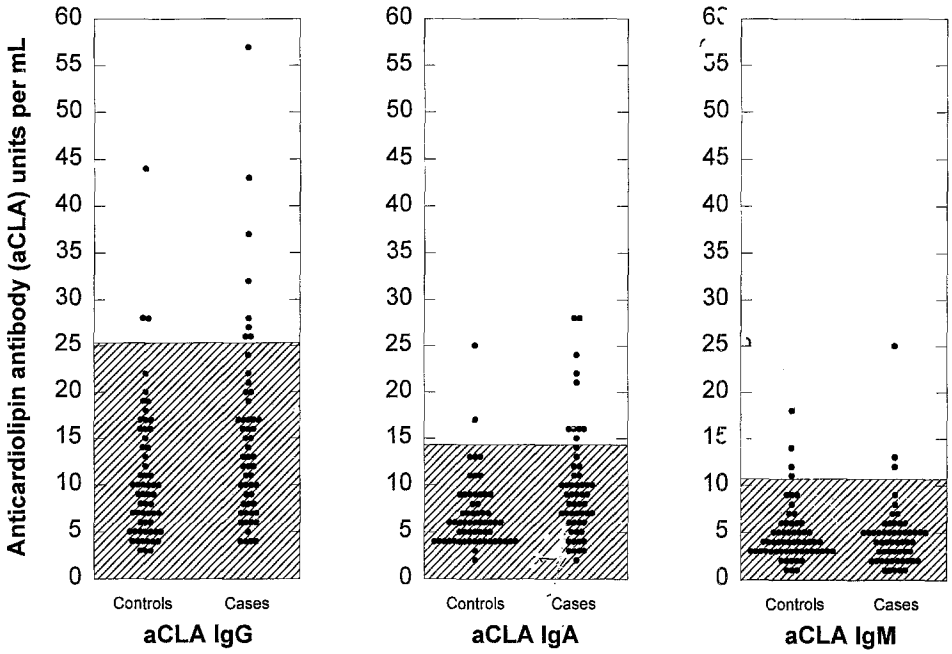

Fig. 1. aCLAs of classes IgG, IgA, and IgM measured by ELISA in 55 patients with osteonecrosis of the jaw. The *hatched area* represents less than 2 SD of the mean of the control subjects, chosen as the cutoff level for positivity. The difference in the patients' values as compared with those of the control subjects (n = 60) was significant for aCLA IgG ($p = 0.01$) and aCLA IgA ($p = 0.001$) but not for aCLA IgM ($p = 0.7$) (Mann-Whitney rank sum test).

dominantly not normally distributed,[23] and nonparametric analyses appropriate to the nature of the distribution were carried out.[24] Chi square analyses, Fisher's exact chi square, Mann-Whitney rank sum tests, and nonparametric Spearman univariate correlations were used.[24]

RESULTS

Clinical and dental characteristics of patients. Median age of the 55 patients (50 women, 5 men) was 46 years, with a range of 17 to 75 years. None of the 55 patients had evidence of diseases that could predispose to secondary osteonecrosis, such as sickle cell trait, alcoholism, major trauma (fracture), or systemic lupus.[16,19-22] Seven patients had received long-term (>1 month) corticosteroid therapy (after onset of their jaw symptoms) that failed to ameliorate their jaw or atypical facial pain.

None of the patients had evidence of suppurative osteomyelitis, although one patient had at one time received intravenous antibiotics for therapy of presumptive osteomyelitis. None of the patients exhibited any signs of active infection at the time that we measured their fibrinolytic and thrombophilic profiles.

The median age of onset of severe jaw or atypical facial pain was 42 years, with a range of 17 to 72 years. All patients suffered with severe, chronic facial and jaw pain syndromes, and 80% required long-term pain relief with narcotics including oral morphine sulfate and methadone. Fifteen of the 50 women (30%) were receiving supplemental postmenopausal estrogens.

Thrombophilic and hypofibrinolytic defects in patients. Of the 55 patients, only 12 (22%) were entirely normal, with normal levels of aCLA, resistance to APC, protein C, protein S, Lp(a), basal PAI-FX, and tPA-Fx (Table I). The other 43 patients (78%) had one or more tests positive for thrombophilia or hypofibrinolysis (Table I). High aCLA levels were found in 18 (33%) patients, low protein C levels were found in 2 (4%), low protein S levels were found in 2 (4%), resistance to activated protein C was found in 9 (16%), high PAI-Fx levels were found in 10 (18%), low tPA-Fx levels were found in 12 (22%), and high Lp(a) levels were found in 20 (36%) (Table I).

Presence of aCLAs. A thrombophilic defect seen in 18 patients (33%) was the presence of high aCLA levels (Table I). Five patients (9%) had elevated levels of IgG alone, 7 (13%) had elevated IgA alone, and 3 (5%) had elevated levels of IgM alone (Table I). Three patients had elevations of both IgG and IgA (Table I).

Table I. Laboratory values in 55 patients with osteonecrosis of the jaws

					Normal range								
ID	aCLA group	Group	Age (yr)	Sex	<25.4 aCLA IgG (U)	<10.9 aCLA IgM (U)	<14.3 aCLA IgA (U)	≥70 PCAG (%)	≥70 PSAG (%)	<25 Lp(a) (mg/dl)	≥2.28 tPA-Fx (IU/ml)	<26.9 PAI-Fx (U/ml)	≥2 APCR
84		Lp(a)	73	F	7.0	6.8	1.5	85	102	**123**	37.30	9.4	2.20
41		Lp(a)	46	F	21.7	1.3	4.2	98	130	**27**	3.30	13.0	2.69
56		Lp(a)	45	F	9.6	2.9	4.9	122	102	**26**	9.70	25.3	2.20
24		Lp(a)	49	F	12.5	5.0	8.9	126	85	**26**	11.55	6.5	2.97
81		Lp(a)	42	F	7.0	3.2	3.3	180	95	**47**	12.30	0.01	3.15
43		tPA	63	F	6.9	2.3	9.6	132	140	1	**0.90**	17.4	2.58
31		tPA	74	M	4.9	4.3	9.8	138	160	14	**0.31**	23.2	2.39
28		tPA	37	F	4.1	5.1	4.6	140	96	6	**1.74**	18.9	2.62
29		tPA	34	F	18.9	1.8	8.9	89	90	1	**1.71**	21.4	2.75
49		APCR	28	F	10.0	5.3	7.2	87	100	1	3.70	12.3	**1.96**
60		APCR	49	F	12.3	4.2	13.6	92	164	16	3.10	23.9	**1.77**
21		C	39	F	5.5	4.3	6.0	**50**	85	14	11.90	6.2	2.47
66		PAI	55	F	4.4	1.7	3.6	202	92	1	4.10	**31.6**	2.57
4		Mixed	33	M	10.0	3.5	3.7	91	82	1	3.40	**39.6**	**1.96**
30		Mixed	48	F	9.6	5.0	7.2	108	80	**94**	**2.19**	18.0	2.64
40		Mixed	37	F	15.1	4.7	7.8	140	126	11	**1.30**	12.9	**1.91**
46		Mixed	49	M	9.3	0.5	6.8	114	156	**56**	**1.50**	24.4	2.43
47		Mixed	40	F	17.3	1.2	5.7	**68**	100	**45**	5.70	25.3	2.82
48		Mixed	58	F	19.6	1.6	5.0	116	100	**39**	3.70	18.6	**1.82**
53		Mixed	53	F	6.0	5.9	7.4	152	87	**65**	9.90	**28.7**	2.27
55		Mixed	43	F	8.1	6.5	10.3	114	92	23	3.50	**30.5**	**1.99**
61		Mixed	43	F	11.3	5.4	3.2	180	107	**38**	6.00	**27.5**	2.27
64		Mixed	17	F	16.9	3.9	5.6	80	**67**	**84**	**2.20**	21.9	2.25
65		Mixed	44	F	7.5	6.0	3.9	130	**67**	**48**	2.40	**31.8**	2.05
86		Mixed	43	F	9.7	5.0	6.5	98	108	**86**	**1.50**	**72.3**	2.53
6		Normal	56	F	4.4	2.3	8.6	104	166	21	6.66	12.2	2.08
8		Normal	24	F	14.9	5.0	7.9	85	92	1	15.06	5.7	2.20
14		Normal	67	F	8.6	2.5	11.4	89	90	6	11.80	7.6	2.62
20		Normal	38	F	13.4	4.6	12.0	104	140	12	5.80	16.1	2.63
26		Normal	41	F	12.5	3.2	13.2	144	220	17	7.49	26.4	2.56
44		Normal	37	F	16.4	2.4	6.8	130	80	7	8.30	9.0	2.48
45		Normal	41	F	11.5	1.6	2.8	92	79	6	2.40	11.1	2.76
62		Normal	44	F	16.1	3.2	8.3	95	87	9	3.10	22.3	2.72
63		Normal	32	F	11.0	8.4	9.7	148	82	1	8.40	18.8	3.05
85		Normal	44	F	5.7	9.0	8.3	85	174	5	15.10	7.9	2.16
87		Normal	46	F	24.4	5.7	6.5	90	75	1	2.30	22.5	2.87
88		Normal	60	F	16.5	3.8	9.6	126	130	1	23.70	2.5	2.59
3	IgA		61	F	16.6	6.3	**20.9**	73	87	1	9.53	1.8	2.56
5	IgA		60	M	19.7	1.1	**16.3**	88	120	18	6.33	15.4	2.60
25	IgA		56	F	12.0	4.2	**16.1**	114	140	18	4.64	18.0	2.75
50	IgA		50	F	17.2	2.7	**14.4**	144	104	17		9.8	2.60
12	IgA	APCR	45	F	15.9	3.7	**15.5**	81	73	17	8.49	15.4	**1.89**
54	IgA	Mixed	51	F	14.2	4.6	**16.4**	190	106	**29**	15.00	20.9	**1.71**
52	IgA	Mixed	63	F	6.6	3.2	**27.8**	130	100	1	**1.40**	15.4	2.37
23	IgG		46	F	**42.7**	6.4	8.8	87	89	11	2.44	18.4	2.96
13	IgG		39	M	**32.0**	5.1	8.6	114	126	7	9.26	17.4	2.81
7	IgG	IgA	45	F	**26.3**	5.2	**22.2**	90	87	1	4.55	11.6	2.84
42	IgG	IgA	66	F	**27.4**	3.7	**24.3**	99	95	17	14.00	21.6	2.42
59	IgG	Mixed	53	F	**26.0**	2.3	9.6	130	97	**32**	2.80	**29.1**	2.16
57	IgG	Mixed	54	F	**37.1**	1.2	11.1	130	200	**39**	**1.70**	**42.8**	2.82
27	IgG	IgA Mixed	35	F	**57.0**	1.7	**28.0**	140	130	10	**0.37**	**55.8**	2.43
39	IgG	Lp(a)	75	F	**28.3**	5.3	11.9	134	170	**35**	9.70	23.8	2.30
9	IgM	APCR	55	F	21.0	**12.3**	9.7	89	110	1	2.60	2.9	**1.59**
51	IgM	Lp(a)	55	F	4.3	**13.0**	5.8	112	140	**69**	4.60	23.2	2.91
82	IgM	Lp(a)	54	F	7.5	**24.7**	4.3	180	150	**30**	11.50	0.01	2.26

Abnormal values are **boldface.**

PCAG, Antigentic protein C; *PSAC,* antigenic protein S.

IgG ($p = 0.01$) and IgA ($p = 0.001$) were higher in patients than in control subjects (Fig. 1).

The only significant correlation between the aCLA classes and other coagulation measures was between IgA and Lp(a) (Spearman $r = -0.29, p = 0.03$).

Lp(a) levels. Twenty patients, 36% of the cohort, had high Lp(a) levels (Table I) as compared with those in control subjects (18 of 90, 20%) ($X^2 = 4.7$, $p = 0.03$). Of these 20 patients, only 5 had high Lp(a) levels as the sole thrombophilic or hypofibrinolytic defect (Table I). Three patients with high Lp(a) levels also had elevated levels of IgG aCLA. Two patients with elevated levels of Lp(a) had elevated levels of IgM aCLA, and 1 had high IgA. Other defects associated with Lp(a) elevations included low APCR (2), low protein C (1), low protein S (2), and low tPA-Fx (5) (Table I).

tPA-Fx levels. Twelve patients (22%) had low tPA-Fx levels (Table I), a hypofibrinolytic trait that was marginally higher in patients than in control subjects (7%) ($X^2 = 3.04, p = 0.08$).

PAI-Fx levels. Ten patients (18%) had high basal levels of PAI-Fx (Table I), the major inhibitor of fibrinolysis. PAI-Fx was more commonly elevated in patients than in control subjects (8%) ($X^2 = 4.6, p = 0.03$).

APCR. Nine patients (16%) had APCR (Table I), an inherited thrombophilic trait that was more common in patients than in control subjects (0 of 40, 0%) ($p = 0.009$, Fisher's exact test).

Protein C or protein S deficiency. The cohort included 2 patients with antigenic protein C deficiency (4%) and 2 (4%) with antigenic protein S deficiency, as compared with 0 of 36 and 0 of 36 control subjects, respectively, $p > 0.2$ for both. None of the patients with protein C or S deficiency had concurrent elevations of aCLA (IgG) (Table I).

DISCUSSION

Thrombophilic or hypofibrinolytic defects (or both) were found in 78% of patients with osteonecrosis of the jaws, a percentage that is is comparable to that for osteonecrosis of the hip in adults[16] and children.[18,19] One third of the patient cohort had high aCLA (IgG, IgA, or IgM) levels. Other common associated defects included high Lp(a) (36%), low tPA-Fx (22%), high PAI-Fx (18%), and APCR (16%).

Recently there has been increasing interest in aCLAs because of their association with thrombosis[6-9] and osteonecrosis.[10-15] aCLAs belong to a family of autoantibodies called *antiphospholipid* antibodies, which are directed against antigens that are composed, at least in part, of negatively charged phospholipids.[6-8] Besides aCLA, clinically important antiphospholipid antibodies include the lupus anticoagulant and antibodies responsible for the false positive VDRL (syphilis) test. Although the name *antiphospholipid antibody* implies that the antibodies are directed toward phospholipid, the true antigenic determinants are probably more complex.[6-8] Although the mechanisms whereby antiphospholipid antibodies cause hypercoagulability are not known, several theories attempting to explain this pathogenesis have been proposed. Possible pathologic mechanisms include inhibition of prostacyclin synthesis, impairment of the thrombomodulin-protein C-protein S anticoagulant system, antiendothelial cell antibodies, or interaction with platelet membrane phospholipids.[6-8] It is possible that some of the 9 patients with APCR (16% of the cohort) could have had the (unmeasured) lupus anticoagulant that may selectively inhibit the protein C pathway.[20] However, in regard to thrombophilia as a pathogenesis for osteonecrosis of the jaws, it may not make a pathophysiologic difference whether APCR is caused by a heritable mutation in coagulation factor V (factor V Leiden) or instead reflects selective inhibition of the protein C pathway by the lupus anticoagulant.[20]

In a similar fashion, the lupus anticoagulant can inhibit the protein S pathway, and it might have accounted for low protein S levels in the 2 patients in whom it was found.

Laboratory assays for aCLA require a protein called beta 2-glycoprotein I, formerly termed *apolipoprotein H*[25]. Beta 2-glycoprotein I is an apolipoprotein that binds avidly to negatively charged phospholipids and may be involved in a variety of important biochemical pathways in vivo, such as the inhibition of platelet activation and coagulation.[25,26] It has been postulated that circulating aCLA may bind to the antigenic sites on the beta 2-glycoprotein I molecule and interfere with the ability of beta 2-glycoprotein I to inhibit the generation of factor X_a by activated platelets, thus creating a hypercoagulable tendency in the blood.[27]

A striking clinical constellation termed the *antiphospholipid syndrome* features the association of aCLA or the lupus anticoagulant, thrombosis, fetal wastage, and thrombocytopenia.[8,9] The lupus anticoagulant is more commonly associated with venous thrombosis, whereas aCLAs are commonly associated with both arterial and venous thrombosis, including typical deep vein thrombosis and pulmonary embolus, premature coronary artery disease, premature cerebrovascular disease, and arterial vascular disease.[8,9,27] This clinical syndrome of vasoocclusive

disorders may result from an immune-mediated disruption of endothelial function,[28] because cross-reactivity between phospholipids and endothelial cells has been demonstrated, as well as circulating antibodies to endothelial cells. Antibodies to endothelial cells and aCLA acting synergistically could damage the endothelium and perpetuate inflammatory, vasoactive, and procoagulant mechanisms.[28] All three aCLA classes (IgG, IgA, and IgM) are associated with thromboses.[6,8] What roles the injured sinusoidal endothelium of alveolar bone in NICO[1,2] play in these immunopathologic reactions remains to be investigated.

Besides venous and arterial thrombotic disorders, aCLAs have been associated with a variety of neurologic syndromes including transient cerebral ischemic attacks, migraine headaches, chorea, seizures, and optic neuritis.[29-32] To our knowledge, aCLAs have not been previously associated with trigeminal neuralgia or other facial pain syndromes.

The association of aCLAs with NICO is of particular interest because of the possible pathogenetic association of vascular occlusion in patients with osteonecrosis of the jaw,[1-3] osteonecrosis of the hip in adults,[16,33-35] and osteonecrosis of the hip in children.[18,19] Antiphospholipid antibodies have been linked to avascular necrosis of bone in other clinical settings.[10-15] In a study of 800 patients with systemic lupus, 37 (4.6%) had symptomatic osteonecrosis, and 27 of these 37 patients were positive for antiphospholipid antibodies (73%)—compared with an overall prevalence of antiphospholipid antibody positivity of about 30% to 40% in the general lupus population.[14] Although the use of oral glucocorticosteroids in many of these patients was a confounding factor, the association of antiphospholipid antibody with avascular necrosis appeared independent.

There is now substantial evidence that osteonecrosis of the femoral head in adults and Legg-Perthes disease in childhood (pediatric idiopathic osteonecrosis) are related to an underlying thrombophilia (increased tendency toward intravascular thrombosis) or hypofibrinolysis (reduced ability to lyse thrombi) in a majority of patients.[16,18,19,33-35] Specific plasma defects associated with thrombophilia and hypofibrinolysis in these osteonecroses include the following: (1) low levels of tPA-Fx, the major stimulator of fibrinolysis, often accompanied by high levels of PAI-Fx, the major inhibitor of fibrinolysis, leading to hypofibrinolysis[16-19,33-35]; (2) low levels of the antithrombotic proteins C or S, leading to unopposed prothrombotic effects of factors Va and VIIIa (thrombophilia)[16-19,33,34]; (3) resistance to activated protein C,[3,36,37] a normal anticoagulant protein that opposes the prothrombotic effects of factor Va (thrombophilia); resistance to activated protein C is the most common risk factor for venous thrombosis and is associated with a mutation in coagulation factor V (factor V Leiden)[36,37]; (4) high levels of the atherogenic, hypofibrinolytic lipoprotein Lp(a).[16-19,33,34,38]

In children and adults with osteonecrosis of the hip, it has been postulated that thrombophilia and hypofibrinolysis facilitate venous occlusion of the bone by fibrin clots, leading to venous (sinusoidal) hypertension within the cancellous bone.[16-19,33-35,38] Once the "ischemic threshold" is reached, cellular hypoxia presumably gives way to bone and marrow cell death. Therapy with stanozolol, an anabolic-androgenic steroid (Winstrol; Winthrop Laboratories) that can normalize PAI-Fx, tPA-Fx, and Lp(a) when given before irreversible cortical collapse of the head of the femur, may reverse hypofibrinolysis, facilitate normal venous drainage, relieve hypoxia/anoxia of the bone, and ameliorate osteonecrosis.[38]

Although NICO has well-documented histopathologic features that are unique and diagnostic for this alveolar pathosis,[1,2] heretofore there has been no uniformly recognized pathogenesis. Chronic dento-alveolar infections and persistent inflammatory conditions probably set the stage by progressively compromising the microvasculature and the flow of blood through the cancellous bone.[39-41] Even when these locally destructive processes are eliminated, systemic and heritable risk factors may further impair cellular health[42-44] and neoangiogenesis so crucial to normal repair and regeneration.[45] Innate pathophysiologic mechanisms that create an increased tendency for blood to coagulate or a reduced ability to lyse thrombi may be enough to persistently generate thrombi in tissues already vascularly compromised.[16-19,33-35]

Our current study reveals that aCLA, frequently in association with other thrombophilic or hypofibrinolytic plasma protein defects, is associated with osteonecrosis of the jaw. We postulate that these thrombophilic and hypofibrinolytic risk factors play a pathophysiologic role in osteonecrosis of the jaw, as they do in idiopathic osteonecrosis of the hip in adults and in children.[16-19,33-35] We also suggest that to ameliorate the pain in patients with NICO who have these hypercoagulable tendencies, therapy with Stanozolol,[38] which may normalize high PAI or high Lp(a) and may reverse the osteonecrotic process, may be helpful before surgery[38] to allow for the best regenerative effort while possibly preventing thrombosis or hypofibrinolysis.

Long-term follow-up studies report 73% to 80%

success in relieving the neuralgic pain of NICO when surgical curettage of the diseased jawbone is carried out in a prescribed manner.[46,47] Beyond the coagulation defects and high aCLA, predisposing to hypercoagulability, additional risk factors associated with the development of avascular necrosis of the jaws are presumed to be similar to those associated with secondary osteonecrosis of other bones, such as in corticosteroid use, systemic lupus erythematosus, sickle cell disease, alcoholism, and trauma, among others.[16,18,19,21,22] We postulate that patients with NICO with these abnormalities *alone* (which potentiate secondary osteonecrosis) can be treated in a predictable manner with surgery alone. In patients with NICO with elevated aCLA and thrombophilia or hypofibrinolysis (or both), surgery alone often results in treatment failure, as in this cohort. Surgical curettage will often improve the pain temporarily, but as long as there is a systemic thrombophilic-hypofibrinolytic risk factor present, we speculate that the venostasis is likely to recur as the cancellous bone attempts to regenerate. Presuming thrombophilia and hypofibrinolysis to be pathogenetic for NICO,[3] as in adult and pediatric idiopathic osteonecrosis,[16-19,33-35] it may be possible, extrapolating from the limited experience with osteonecrosis of the hip,[38] to reverse the hypofibrinolysis with Stanozolol. In the early stages of osteonecrosis, Stanozolol therapy, by normalizing fibrinolysis (lowering PAI and Lp[a], and elevating tPA-Fx), may facilitate resumption of normal venous drainage, reduction of intramedullary venous hypertension, resumption of normal osseous oxygenation, and cessation of bone necrosis. Venous thrombosis associated with heritable thrombophilia, including resistance to activated protein C and deficiency of protein C or protein S, can be treated with coumadin,[49] as can elevated aCLA.[49] Whether such therapies will have a beneficial effect on ameliorating the pain and recurrent osteonecrosis in these patients with difficult-to-treat NICO is the subject of another ongoing investigation. In the meantime, many of these patients require full support from a multidisciplinary pain center, including adequate narcotic medications.

Conclusion. Our current study suggests that aCLAs in association with other thrombophilic or hypofibrinolytic plasma defects may play a pathogenetic role in the "idiopathic" osteonecrosis seen in patients with NICO that is similar to their role as pathophysiologic risk factors for idiopathic femoral head necrosis in adults and children. aCLAs are elevated in one third of patients with osteonecrosis of the jaw, while elevated Lp(a) levels, low tPA-Fx, high PAI-Fx, and APCR are common associated defects. Thrombophilia may contribute not only to the genesis of atypical facial neuralgia seen in patients with osteonecrosis of the jaw but also to the treatment failures so often encountered in such patients.

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