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Lipoprotein (a), Birth Weight and Neonatal Stroke

Cyrille Renaud[a, b] Christine Bonneau[c] Emilie Presles[a, b]
Silvy Laporte[a, b] Arnaud Depeyre[b] Marie-Noëlle Varlet[b, d]
Stéphane Chabrier[b, e] for the AVCnn group

[a]Groupe de recherche sur la thrombose, EA 3065, Université Saint-Etienne, [b]Inserm, CIE3, et [c]Service de biochimie, [d]Service de gynécologie obstétrique et [e]Service de néonatologie et réanimation pédiatrique, Hôpital Nord, CHU Saint-Etienne, Saint-Etienne, France

Key Words
Neonatal stroke · Lipoprotein (a) · Birth weight · Vascular placental pathology

Abstract
Background: Elevated lipoprotein (Lp) (a) is the most common genetically determined risk factor found in babies with perinatal ischemic stroke. The influence of maternal Lp(a) has not been studied extensively to date. ***Objectives:*** To investigate the role of Lp(a) in our population of neonates with stroke. ***Methods:*** In a prospective uncontrolled cohort of term-born children with neonatal arterial ischemic stroke, Lp(a) levels were investigated in 69 mothers and 69 children. Paternal Lp(a) was not explored. ***Results:*** An increased Lp(a) level was found in 26 mothers [38%; 95% confidence interval (CI) 28–50%] and in 15 children (22%; 95% CI 13–33%). Both rates were higher than the reference range reported in the general Caucasian population (10% in adults and 5% in children). Additionally, there was a correlation between maternal and infantile Lp(a) levels ($p < 0.0001$) and between elevated maternal Lp(a) level and lower birth weight ($p = 0.027$). ***Conclusions:*** Elevated maternal Lp(a) is apparently a risk factor for neonatal arterial ischemic stroke. We speculate that the pathological mechanism of this relation may be mediated through a dysfunction of the placental vascularization.

Introduction

Although perinatal ischemic stroke is the most frequent form of pediatric stroke, many questions remain unsolved regarding the causes and mechanisms of this disease. Previous studies have shown that many thrombophilic factors (either carried by the mother or the baby) are risk factors for perinatal arterial ischemic stroke (AIS), and among them elevated lipoprotein (Lp) (a) is the most commonly implicated risk factor [1–3]. The mechanism by which these risk factors lead to stroke is not completely understood.

Lp(a) is a specific class of lipoprotein particles made up of a single copy of apolipoprotein B-100 linked to an apolipoprotein(a) component. Its structural homology to plasminogen may lead to inhibition of fibrinolysis, contributing to a thrombogenic milieu. A recent meta-analysis of observational studies in adults indeed confirmed that elevated Lp(a) levels correlate with cardiovascular risk, notably myocardial infarction and stroke [4].

Methods

This study is part of an ongoing project, the AVCnn study (for accident vasculaire cérébral du nouveau-né, i.e. neonatal stroke), aimed at compiling a large database dedicated to risk factors and outcome of neonatal stroke. The experimental plan is a prospec-

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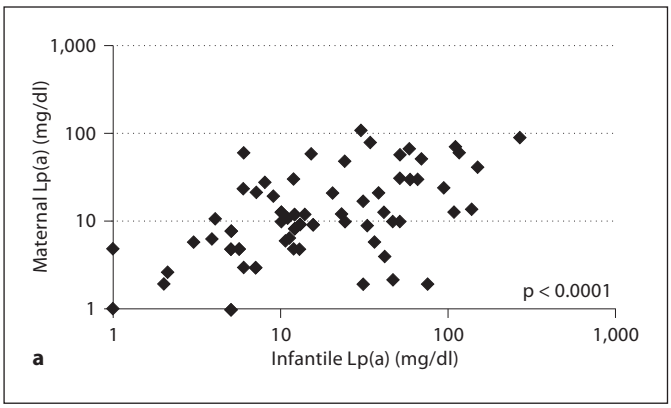
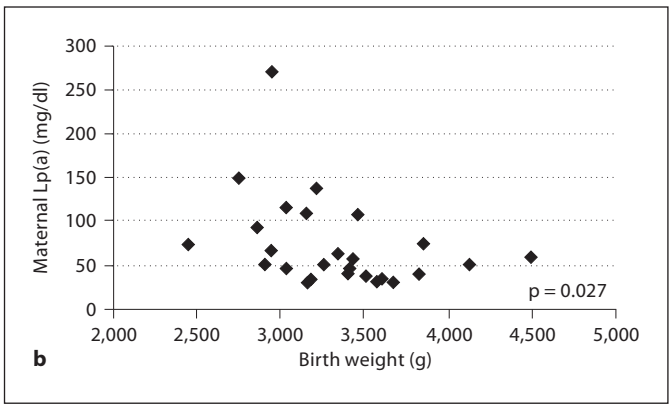
Stéphane Chabrier, MD
Service de néonatologie et réanimation pédiatrique
Hôpital Nord, CHU Saint-Etienne, FR–42055 (France)
Tel. +33 477 828 729, Fax +33 477 828 108
E-Mail stephane.chabrier@chu-st-etienne.fr





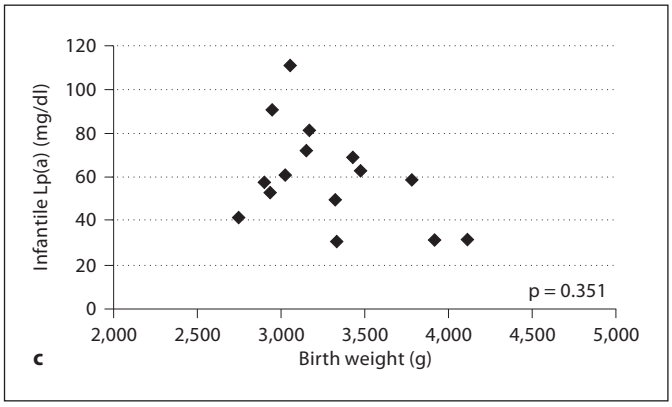


Fig. 1. Relation between maternal and infantile Lp(a) levels (**a**) and between birth weight and maternal (**b**) and infantile (**c**) elevated Lp(a) levels. p values are the results of Spearman's rank correlation test. Only in mothers is a lower birth weight statistically associated with higher Lp(a) levels.

tive multicenter uncontrolled cohort study. The study was approved by the ethics committee of the Centre hospitalier universitaire de Saint-Etienne and parental consent was obtained for all children.

In brief, term newborns with symptomatic AIS were consecutively recruited from November 2003 to October 2006 in 39 centers distributed all over France [5]. Of the entire cohort of 100 enrolled children, 2 babies died in the neonatal period and, to date, four families have been lost to follow-up. The other babies are regularly followed up with a preestablished standardized program of clinical and biological investigations. Thrombophilia testing (antithrombin, protein C, S and Z activities, presence of antiphospholipid antibodies and mutation of factors II and V, Lp(a) and homocysteine plasma levels) for the mother/child pair – but not the father – was planned at the 12 months' follow-up appointment.

This paper focuses on Lp(a). Biochemical analyses were performed in the local laboratory using an immunonephelometric (n = 129) or a turbidometric assay (n = 9). As previously defined in several case-control studies in adults and children with cardiovascular diseases [4, 6], the serum Lp(a) level of >30 mg/dl was set as a risk threshold value in the present family-based survey.

Apart from descriptive analyses (median, minimum-maximum values, percentages), correlations were determined by Spearman's rank correlation test. Confidence intervals (CI) were calculated using the exact binomial method.

Results

Lp(a) analysis was available in 69 children and 69 mothers. In 4 cases the mother was investigated while the child was not investigated, and vice versa. Thus, a complete set of studies was done for 65 mother/child pairs. There were no differences in family history, pregnancy, delivery conditions and neonatal demographic data between those who were investigated and those who were not investigated (data not shown).

Maternal Lp(a) ranged from <5 to 270 mg/dl (median 13 mg/dl) and was above the cutoff of 30 mg/dl in 26 cases (38%; 95% CI 28–50%). In the infants, Lp(a) ranged from <5 to 111 mg/dl (median 12 mg/dl), with 15 cases (22%; 95% CI 13–33%) above 30 mg/dl. Of the 65 mother/child pairs, Lp(a) values in 45 (69%) were in agreement [i.e. the child and the mother were similarly classified as having or not having an elevated Lp(a)]. Moreover, there was a strong correlation between the maternal and infantile Lp(a) level ($p < 0.0001$; fig. 1). Among the 20 discordant pairs, 15 mothers had elevated Lp(a) concentrations while their children remained within the normal range,

and 5 children had elevated Lp(a) concentrations while Lp(a) in their mothers was normal. Finally, Lp(a) was elevated in either child, mother, or both in 30 of the 65 pairs (46%; 95% CI 34–59%).

We also noted a negative correlation between the elevated maternal Lp(a) level and birth weight ($p = 0.027$; fig. 1).

Discussion

In the present cohort study in term-born children suffering from neonatal AIS we focused on the role of elevated Lp(a) in 65 mother/child pairs. Increased Lp(a) was found to be the most frequently established genetic risk factor in our population. The data reported here are in line with previous reports in white children with perinatal AIS [1–3]. In the German cohort study, for example, Lp(a) was found to be elevated in 30% of cases compared with 5% in healthy population-based controls [1]. In addition, the rate of a maternal elevated Lp(a) concentration of 38% reported by us is similar to the rate of 33% published in 2007 by Curry et al. [2] in 24 mothers of children with neonatal or presumed perinatal AIS, underlining the important association between elevated Lp(a) concentrations and the risk of perinatal AIS. The further role of maternal genetic risk factors has received less attention, although two recent studies reported a higher prevalence of thrombophilia in mothers than in children [2, 7]. Lp(a), however, was not investigated in the study carried out in Israel [7].

We also observed a strong correlation between maternal and infantile Lp(a) levels and a negative correlation between the maternal elevated Lp(a) concentration and birth weight. This is not surprising, since heritability estimates of elevated Lp(a) concentrations have ranged from 0.75 to 0.98. The apo(a) gene (and notably the numbers of its kringle 4 repeats) is the major gene influencing the Lp(a) level [8]. It has also been shown that either maternal or fetal thrombophilia increases the rate of obstetric complications. Moreover, normal pregnancy itself is an acquired hypercoagulable state. The association with genetic thrombophilia may thus lead to further placental thrombosis and insufficiency, which therefore confers a higher risk of intrauterine growth retardation and for the development of maternal and fetal morbidity, including perinatal stroke through placentocerebral embolism. The theory of Lp(a)-induced pregnancy complications, such as recurrent miscarriage or susceptibility to preeclampsia, is in line with this concept of disturbed placental circulation [9]. Thus, the increased rate of 38% Lp(a) found in our maternal cohort may suggest a similar pathological mechanism through impaired vascular placental function. Furthermore, in a recent Spanish study it was reported that the lipid profile [including Lp(a)] in adolescents is related to weight at birth [10]. The authors concluded that polymorphisms in the genomic region encoding the apolipoproteins influence the association between low birth weight and blood lipid levels.

Our data and those of others suggest the possibility of different mechanisms of AIS in children of different birth weight: those with a lower birth weight suffer from vascular placental insufficiency during pregnancy and those with a higher weight are more at risk of an acute event during the birthing process [2, 5, 11]. The negative correlation between an elevated Lp(a) level and birth weight is (1) in line with the hypothesis that a cerebral embolism originating from a pathological placenta (eventually related to a thrombophilic milieu) is more prone to be the privileged pathological mechanism in lighter than in larger babies. On the other hand, (2) epidemiological studies also suggest an association between preeclampsia and intrauterine growth retardation and an increased risk of future cardiovascular diseases [12, 13]. Shared constitutional risks for maternal vascular-related pregnancy complications and cardiovascular disease such as elevated Lp(a) may explain part of this relationship. For a mother, the fact of having a child with perinatal AIS can be considered as the first episode of *her* cardiovascular history. In addition, (3) there is increasing evidence indicating that low birth weight is a risk factor for cardiovascular disease in adulthood [10]. The intrauterine environment is thus suggested to interact with the genetic background affecting the cardiovascular risk profile later in life. The inverse hypothesis (i.e. confounding constitutional factors that lead to low birth weight and thrombotic diseases as early as in the neonatal period) must also be considered.

The limitations of the present study include first the lack of a population-based pediatric control group. On one hand, however, the prevalence of Caucasian adults with Lp(a) concentrations >30 mg/dl is approximately 10%, clearly less than the inferior 95% CI boundary found in our maternal cohort (28%). In a comparable white population (i.e. 133 young German Caucasian women aged 17–40 years) a prevalence of 10.5% Lp(a) elevation was found [9]. Interestingly, this prevalence rose to 33% in an age-matched population of women who had suffered from unexplained recurrent miscarriages [9]. On the other hand, from a pediatric point of view we have to take into account the progression of the Lp(a) concentration during the first 12 months of life: therefore, the basal rate of ele-

vated Lp(a) in infants is lower, close to 5% in a healthy European population [1, 6]. This is clearly below the 95% CI inferior limit found in our pediatric cohort (13%). Second, another limitation of our study is the small sample size of patients with elevated Lp(a), notably of infants. The correlation between low birth weight and elevated maternal Lp(a) concentration should thus be interpreted with caution and may represent a fortuitous statistically significant result. Nevertheless, as discussed above, this correlation is consistent with previous reports [2, 5, 10, 11].

In conclusion, we support in our cohort the hypothesis that the maternal elevated Lp(a) concentration is a risk factor for neonatal AIS. This relation may be mediated through placental dysfunction. Future large studies are needed to investigate the relation between Lp(a) concentration and obstetric-neonatal conditions and its link with future cardiovascular events in mothers and their children.

Appendix

Members of the AVCnn Group

H. Testard (Annemasse), J. Nzonzila, K. Othmani (Aulnay-sous-Bois), M. Boutrolle, J.P. Laboureau (Auxerre), S. Lamoureux-Toth, P. Masson (Avignon), H. Apéré, P. Jouvencel, S. Rivera (Bayonne), L. Razafimanantsoa (Beauvais), G. Thiriez (Besançon), E. Lachassine, C. Mignot (Bondy), F. Audic-Gérard, S. Brochard, V. Laparra, J. Lefranc, S. Peudenier (Brest), T. Lecine (Cahors), N. Meier (Carcassone), S. Gay, R. Matta (Chalon-sur-Saône), V. Gajdos (Clamart), B. Lecomte (Clermont-Ferrand), M. Raqbi, L. Tahraoui (Creil), C. Barnérias, I. Layouni, N. Yousef (Créteil), N. d'Heilly, M. Granier (Evry), P. Saunier (Fontainebleau), F. Cneude (Grenoble), P. Landrieu, V. Legrez, M. Tardieu (Le Kremlin-Bicêtre), V. Pierrat (Lille), E. Agudze, C. Laroche (Limoges), D. Ville (Lyon), P. Garcia-Méric (Marseille), A. Roubertie (Montpellier), M. Bru, S. Nguyen The Tich, J. Perrier (Nantes), M.C. Routon (Orsay), L. Delour, S. Mallet (Périgueux), Y. Aujard, C. Farnoux, I. Husson, M. Rajguru, C. Saizou (Hôpital Robert Debré, Paris), M. Mokhtari, F. Villega (Hôpital Saint-Vincent-de-Paul, Paris), T. Blanc, A. Charollais, S. Marret (Rouen), J.M. Retbi, P. Bolot (Saint-Denis), S. Chabrier (Saint-Etienne), E. Cheuret, I. Glorieux, N. Montjaux, S. Lebon, J.Y. Le Tallec (Toulouse), Y. Lakhdari, E. Saliba (Tours), N. Benbrik, D. Soupre (Vannes), A. Cailho, C. Coudy (Versailles), C. Ringenbach (Villefranche-sur-Sâone), N. Blanc, M.J. Boivin, F. Guillot (Villeneuve-Saint-Georges) as local clinicians.

D. Allard, B. Husson (radiology), M.N. Varlet (obstetrics), B. Tardy (hemostasis).

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