Original articles

J. Perinat. Med.
17 (1989) 195

Enzyme variability and neonatal jaundice. The role of adenosine deaminase and acid phosphatase

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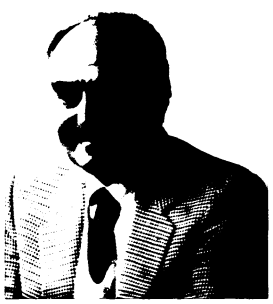
1 Introduction

In a recent paper we have reported an interaction between ACP_1 (Erythrocyte acid phosphatase EC 3.1.3.2.) and ADA (Adenosine deaminase EC 3.5.4.4.) in relation to neonatal hyperbilirubinemia. The incidence of jaundice was much higher among newborn of ACP_1 phenotype BA carrying ADA^2 allele (41.7%) than among other infants (7.5%) [3]. We have now studied a new series of infants from another population: the data confirm that ACP_1 phenotype BA carrying ADA^2 allele has a very high risk of clinically relevant neonatal jaundice.

It is likely that both environmental and genetic factors influence the severity of "physiologic jaundice of newborn". As in many pathologic situations in which a multifactorial inheritance is presumed, research should be directed toward those factors which determine the "normal variability" of biochemical and physiological parameters. Human genetic polymorphisms are therefore the most important candidates for this kind of investigations.

ACP_1 is an enzyme found in the cytoplasm of many tissues besides red blood cells. It is genetically distinct from acid phosphatases found in lysosomes and is polymorphic with three codominant alleles (P^A, P^B and P^C) at an autosomal locus [11, 12, 20]. ACP_1 probably acts in vivo as a flavin mononuclectide phosphatase [14, 15, 17]. It may therefore modulate Krebs-cycle activity and other important enzymes such as glutathione reductase, a flavoenzyme which exert a key role in the maintenance of red cell integrity [17]. Enzymatic activity of ACP_1 is modulated (activated or inhibited) by purines and inhibited by folic acid. The most important aspect of these findings is the fact that in the quantitative variation of ACP_1 enzyme activity, the contribution of the alloenzymes increases in the order $P^A < P^B < P^C$ [12] whereas with the effects on purine and folic acid modulation, the alloenzyme contribution is ranked either

Curriculum vitae



ALESSANDRO LEPORE, *M. D. was born in 1930. As medical student, he prepared his thesis in the Mendel Institute of University of Rome under the direction of Prof.* LUIGI GEDDA *and received his M. D. "magna cum laude" in 1956. Dr.* LEPORE *is specialized in Gastroenterology and Hygiene. He has been Director of the Center for Hygiene and Preventive Medicine of U. L. S. S. of Penne and his main interest is Community Medicine.*

$P^C < P^A < P^B$ or $P^B < P^A < P^C$. This difference in ranking indicates that the two types of activity variation represent independent effects [14].

The association previously reported [5, 6, 8] between CA phenotype and neonatal hyperbilirubinemia has been tentatively explained by the fact that activation of CA by adenine is stronger as compared to other ACP_1 genotypes. This would cause a reduced availability of flavin cofactors (figure 1) and a lower activity of the flavo-enzyme glutathione reductase which in turn may be reflected in a reduced red cell stability [14]. Since flavoenzymes have a central role in metabolism, modulation of coenzyme levels may have importance in many developmental processes which may influence bilirubin metabolism. Recent observations by our group seem to give support to this conjecture [2, 4].

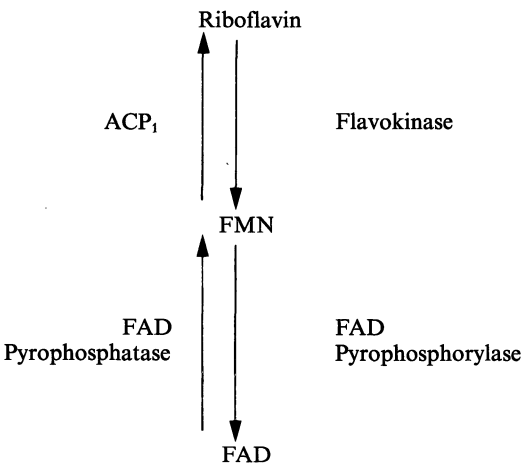


Figure 1. Scheme showing the action of ACP_1 on flavin cofactors metabolism. (Slightly modified from Mansfield and Sensabough [14].)

ADA is a polymorphic enzyme which catalizes the deamination of adenosine to inosine. Its synthesis is controlled by an autosomal locus with two codominant alleles ADA^1 and ADA^2. The enzymatic activity decreases in the order $ADA^1 > ADA^2$ [1, 9, 19]. The study of possible interactions between ACP_1 and ADA was suggested by the observation that while adenosine does not show appreciable effects of ACP_1 activity, inosine, on the contrary, is a relatively strong activator [14].

2 Material and methods

2.1 Infants from the population of Penne

Penne is a small town in the East Side of Southern Italy. It is located in a rural area, at a distance of about two hundred kilometers from Rome. The population is very homogeneous and immigration is practically absent. These people are probably the direct descendants of the ancient Italic population called "VESTINI".

A sample of 56 children treated by phototherapy during the neonatal period (53% of infants observed in four years) were studied. All children were born at term and weighted 2500 grams or more. Phototherapy was started at bilirubin level of 12 mg/dl. The proportion of full term infants treated by phototherapy is about 15% in this population.

A control sample of 141 newborn infants without clinically relevant neonatal jaundice were also studied.

2.2 Newborn infants from the population of Rome

This sample has been already reported in a previous paper [3]. Two consecutive series of infants, born at term, weighting 2500 gr or more and compatible with their mothers in ABO and Rh systems, were studied. Both ADA and ACP_1 phenotypes were determined in 225 infants. Twenty one (9.33%) were treated by phototherapy. In these subjects, therapy was started at bilirubin levels greater than 12 mg/dl.

ACP_1 and ADA phenotypes were determined by starch gel electrophoresis [12, 19] on umbilical cord blood (Rome) or venous blood (Penne).

3 Results

Table I shows the sample distribution of some relevant variables in infants with neonatal jaundice. In the sample from Penne, maternal age distribution is shifted towards extreme values.

Tables II and III and figure 2 show that in both populations BA phenotype carrying ADA^2 allele is associated with a very high incidence of clinically relevant neonatal jaundice. However, besides this striking similarity of the ACP_1 by ADA interaction in relation to neonatal jaundice the data also show differences between the two populations. In fact ACP_1 phenotype BA not carrying ADA^2 shows an incidence of jaundice much higher in the pop-

Table I. Jaundiced infants treated by phototherapy during neonatal period from two Italian populations. Sample distribution of some relevant variables

		Population	
		Penne	Rome
Number of infants		56	21
Sex proportion % (males/total)		51.8	52.4
Gestational age (weeks)	mean	39.80	40.09
	S. D.	0.84	1.84
Birth weight (grams)	mean	3482	3476
	S. D.	431	451
Maternal age	$\leqslant$25 years %	46.4	38.1
	25–35 years %	33.9	47.6
	$\geqslant$35 years %	19.8	14.3

Table II. Joint distribution of ACP_1 and ADA phenotypes in jaundiced and in not-jaundiced infants

		Population							
		Penne				Rome			
		Treated infants ADA^2 allele		Untreated infants ADA^2 allele		Treated infants ADA^2 allele		Untreated infants ADA^2 allele	
		absent	present	absent	present	absent	present	absent	present
ACP_1 phenotype	A	4	/	9	2	1	/	23	1
	B	17	2	62	9	9	2	82	14
	C	/	/	/	/	/	/	/	1
	BA	19	7	38	5	1	5	54	7
	CA	3	/	5	1	1	/	2	1
	CB	3	1	9	1	2	/	16	3

Table III. Incidence of jaundice in ACP_1 phenotype BA in relation to presence of ADA^2 allele. In the sample from Penne the incidence was estimated taking into account the phenotype distributions in treated and not-treated infants and the mean incidence of jaundice in newborn infants. For independence tests actual number of observations were used

	BA not carrying ADA^2	BA carrying ADA^2	Other ACP_1 phenotypes	Whole sample	Significance (Chi) square test of independence)
Rome	1.8%	41.7%	9.5%	9.3%	0.001
Penne	18.2%	38.4%	12.0%	15.0%	0.025

Three way contineency table analysis by log-linear model [18]
X = ACP_1-ADA joint phenotype FACTOR (categories: ACP_1 BA-ADA^2 carrier/other types)
Y : JAUNDICE FACTOR (categories: treated by phototherapy/not treated)
Z = POPULATION FACTOR (categories: Penne/Roma).

test	G (Williams)	D. F.	Significance
X-Y-Z interaction	0.828	1	N. S.
independence of factors X and Y given the level of Z	14.574	2	<0.001
independence of factors X and Z given the level of Y	1.380	2	N. S.

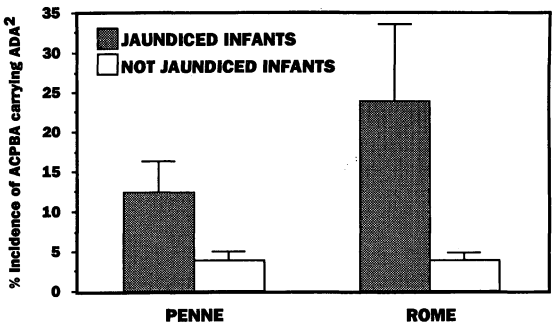


Figure 2. Incidence of ACP_1 phenotype BA carrying ADA^2 allele among jaundiced and not jaundiced infants. Vertical lines represent standard errors.

ulation of Penne than in the population of Rome. These differences may be due: (i) to ethnics background, (ii) to differences in the clinical approach especially in the administration of phototherapy, and (iii) to the possibility that jaundiced infants excluded for sampling have slightly different clinical characteristics as compared to infants included in the study.

In the sample from Rome the risk of neonatal jaundice is 41.7% for ACP_1 BA infants carrying ADA^2 and 7.5% for other infants. Relative risk for ACP_1 BA infants carrying ADA^2 is 5.55 and attributable risk is 34.2%. In the sample from Penne and indirect estimate gives a risk of neonatal jaundice of 38.4% for ACP_1 BA infants carrying ADA^2 and 13.8% for other infants. Relative risk is 2.78% and attributable risk 24.6%.

4 Discussion

The present data make it extremely unlikely that the observed combined effect of ACP_1 and ADA phenotypes on the incidence of neonatal jaundice may be due to sampling chance phenomena. Since the population of Penne is homogeneous, stratification can be reasonably excluded.

The positive association of jaundice with ACP_1 phenotype CA previously reported by our group may be explained assuming that, since CA has a relatively high activity, flavin cofactors and glutathione reductase activity are reduced. This in turn would cause a reduction of RBC survival and an increase of bilirubin load. In subjects carrying ADA^2, however, the highest incidence of neonatal jaundice is observed in ACP_1 phenotype BA. Since ACP_1 BA has a low enzymatic activity and probably a relatively high levels of flavin cofactors, some other mechanism must be assumed in order to explain the association. ADA^2 carriers produce less inosine as compared to ADA 1 subjects and therefore ACP_1 activity may be generally lower in ADA 2-1 than in ADA 1. ACP_1 phenotype BA in the presence of ADA^2 might attain very low enzymatic activities and in turn flavoenzymes and related metabolic pathways might have high levels of activity. It is known that microsomal heme oxigenase catalyses the oxidation of heme at the α-methene bridge to form biliverdin; this step is subsequently coupled with soluble NADPH-dependent biliverdin reductase to form bilirubin [7, 16, 21]. Concentration of cofactors produced by metabolic pathways involving flavoenzymes may be rate-limiting for the heme-oxigenase complex and for the production of bilirubin in the newborns. Heme oxigenase activity and production of endogeneous CO in newborns should be analysed in relation to ACP_1 and ADA phenotype in order to give support to our conjecture.

Ethnic factors may affect the severity of physiologic jaundice in full-term compatible newborns [10, 13]. Table IV shows that the incidence of clinically significant jaundice (serum bilirubin $\geqslant 10-12$ mg/dl) in ABO compatible newborns is much lower in Negro than in White population. In Negro populations the frequency of BA-ADA 2-1 phenotype is about one fifth of that observed in Whites. Assuming that interactions similar to those observed in Italian populations are also acting in the genetic background of Blacks, from the data in table IV one can calculate that more than one third of the difference in the incidence of neonatal jaundice between the two ethnic groups may be explained by the difference in the frequency of ACP_1 BA-ADA 2-1 genotype. The practical absence of ACP_1 phenotype CA in Blacks may also contribute to the low incidence of jaundice in this ethnic group.

Genes for ACP_1 and ADA are on chromosomes 2 and 20 respectively; therefore, no linkage effects are involved in the interaction between these polymorphisms.

The possibility that effects on jaundice may be due to genes linked to ACP_1 and/or ADA cannot be excluded at present. However, since the functions of ACP_1 and ADA suggest plausible biochemical mechanisms we would favour a direct

Table IV. Frequency of ACP_1 BA-ADA 2-1 phenotype in White and Negro populations and incidence of clinically significant jaundice in newborns compatible in the ABO system

	Approximate % gene frequencies			Expected % frequencies	% Incidence of clinically significant neonatal jaundice				
	P^a	P^b	ADA^2	of ACP_1 BA-ADA 2-1 phenotype	U.S.A. (Friedman)	U.S.A. (Kirkman)	All subjects	Rome ACP_1 BA-ADA 2-1 subjects	Other types
Whites	27	67	7	4.7	13.3	12.5	9.3	41.6	7.5
Blacks (U.S.A.)	20	77	1.5	0.9	7.0	4.4	—	—	—

involvement of ACP_1 and ADA in the phenomenon presently described.

It is likely that metabolic variability due to enzyme polymorphism may significantly contribute to modulation of bilirubin metabolism in the critical phase of adaptation to extrauterine life. Enzyme of purine nucleotide metabolism (including ADA), ACP_1 and flavoenzymes may represent a polygenic complex influencing bilirubin levels in the first few days of life and probably also other developmental variables.

Abstract

A sample of children treated by phototherapy during the neonatal period has been studied in the population of Penne (South Eastern Italy) in order to confirm the association previously reported in newborns from the population of Rome between neonatal jaundice and phenotypes of adenosine deaminase (ADA) and acid phosphatase (ACP_1).
The present data confirm that the incidence of clinically relevant jaundice is much greater in newborns of phenotype ACP_1 BA carrying ADA^2 allele than in other infants.
Since ACP_1 probably acts as flavin mononucleotide phosphatase and is modulated by purine nucleotides, it is likely that enzymes of purine nucleotide metabolism (including ADA), ACP_1 and flavoenzymes (including gluthatione reductase and enzymes of Krebs cycle), may represent a polygenic complex influencing bilirubin levels in the first few days of life.

Keywords: Acid phosphatase, adenosine deaminase, enzyme polymorphism, neonatal jaundice.

Zusammenfassung

Enzymvariabilität und neonatale Gelbsucht — zur Rolle der Adenosin-Deaminase und Säurephosphatase
In früheren Untersuchungen konnte in der Bevölkerung von Rom bei reifgeborenen Kinder mit Blutgruppen-Kompatibilität folgendes Phänomen beobachtet werden: Neugeborene mit ACP_1 Phänotyp BA, Träger von ADA^2-Allelen zeigten häufiger eine Gelbsucht als andere Kinder (ACP_1 = Säurephosphatase Locus 1, ADA^2 = Adenosin-Deaminase). Diese Beobachtung ist nun an einer weiteren Untersuchungsreihe von Kindern aus einer anderen italienischen Population bestätigt worden. Wir untersuchten 56 Kinder, die in der Neonatalphase eine Phototherapie erhielten und 141 Neugeborene ohne Gelbsucht aus der Region von Penne (Südosten von Italien). Zum Vergleich werden die Daten der 225 Kinder aus der römischen Bevölkerung gezeigt.
Tabellen II u. III, sowie Abbildung 2 zeigen, daß in beiden Populationen ACP_1 Phänotyp BA, Träger von ADA^2-Allelen positiv korreliert ist mit einer klinisch bedeutsamen Gelbsucht. Der Anteil der Kinder mit der o. gen. Konstellation an Neugeborenen mit Hyperbilirubinämie betrug in Rom 23.8% und in Penne 12.5%. Bei Kindern ohne Gelbsucht war der Anteil 3.4% bzw. 3.5%.
ACP_1 ist ein polymorphes Enzym, welches wahrscheinlich in vivo als eine Flavin-Mononucleotid-Phosphatase fungiert. Von daher könnte es die Aktivität im Krebs-Zyklus modulieren und andere wichtige Enzyme wie die Glutathionreductase beeinflussen, ein Flavoenzym, das eine Schlüsselrolle bei der Formerhaltung der roten Blutkörperchen spielt. Die enzymatische Aktivität der ACP_1 wird durch Purine moduliert (d. h. aktiviert oder inhi-

biert). Der wichtigste Aspekt dieses Befundes ist die Tatsache, daß bei der quantitativen Variation der ACP_1-Aktivität die Wirkung der Alloenzyme in der Rangordnung $p^a < p^b < p^c$ zunimmt, während hinsichtlich der Modulation der Purine die Wirkung der Alloenzyme mit $p^c < p^a < p^b$ oder $p^b < p^a < p^c$ einzuordnen ist.
ADA ist ein polymorphes Enzym, welches die De-Aminierung von Adenosin zu Inosin katalysiert. Die Synthese wird durch einen autosomalen Locus mit zwei kodominanten Allelen ADA^1 und ADA^2 kontrolliert. Die enzymatische Aktivität nimmt in der Reihenfolge $ADA^1 > ADA^2$ ab. Daß eine Interaktion zwischen ACP_1 und ADA möglich ist, wurde durch die Beobachtung nahegelegt, daß Adenosin keinen bedeutsamen Einfluß auf die ACP_1-Aktivität hat, während dagegen Inosin als relativ starker Aktivator wirkt.
Ethnische Faktoren könnten den Schweregrad einer physiologischen Hyperbilirubinämie bei Reifgeborenen beeinflussen. Tatsächlich ist die Inzidenz einer klinisch bedeutsamen Gelbsucht bei Neugeborenen mit ABO-Kompabilität unter Negern viel niedriger als in der weißen Population. Da die Frequenz von BA-Personen, die ADA^2-Träger sind, unter Schwarzen ebenfalls geringer ist als unter Weißen, könnte dies zu der unterschiedlichen Inzidenz der neonatalen Gelbsucht bei diesen beiden ethnischen Gruppen beitragen (Tabelle IV).
Wahrscheinlich wirkt die metabolische Variabilität, bedingt durch den Enzympolymorphismus, entscheidend auf die Modulation des Bilirubinmetabolismus in der kritischen Adaptationsphase an das extrauterine Leben ein. Enzyme des Purinstoffwechsels (incl. ADA), ACP_1 und Flavoenzyme widerspiegeln einen polygenen Komplex, der die Bilirubinspiegel in den ersten Lebenstagen sowie vielleicht auch andere Variabilitäten in der Entwicklung beeinflußt.

Schlüsselwörter: Adenosin-Deaminase, Enzympolymorphismus, neonatale Gelbsucht, Säurephosphatase.

Résumé

Variabilité enzymatique et ictère néonatal. Role de l'adénosine déaminase et de la phosphatase acide
Des études antérieures sur la population de Rome ont montré que chez les nouveaux-nés compatibles à terme, l'incidence d'ictères chez les nouveaux-nés de phénotype ACP_1 (phosphatase acide locus 1) BA portant l'allèle ADA^2 (adénosine déaminase) est beaucoup plus élevée que chez les autres enfants. Cette observation est maintenant confirmée dans une nouvelle série d'enfants issus d'autre population italienne.
On a étudié un échantillon de 56 enfants traités par photothérapie en période néonatale et un échantillon de 141 nouveaux-nés sans ictère provenant de la population de Penne (Sud Est de l'Italie). A titre de comparaison, les données des séries antérieure de 225 enfant romains sont rapportées.
Les tableaux II et III ainsi que la figure 2 montrent que dans les 2 populations le phénotype ACP_1 BA sortant l'allèle ADA^2 est associé positivement avec lictère néonatal clinique.
Parmi les enfants ictériques la proportion de Phénotype ACP_1 BA portant l'allèle ADA^2 est de 23,8% à Rome et de 12,5% à Penne; Parmi les enfants sans ictère, les proportions sont restpectivement de 3,4% et de 3,5%.
ACP_1 est une enzyme polymorphique qui agit vraisemblablement in vivo comme une phosphatase mononucléotide flavine; elle peut donc moduler l'activité du cycle de Krebs et d'autres enzymes importantes telles que la glutathion réductase, flavoenzyme qui exerce un rôle clé dans la maintenance de l'intégrité des globules rouges. L'activité enzymatique de l'ACP_1 est modulée (activation ou inibition) par les purines. L'aspect le plus important de ces éléments est le fait que pour la variation quantitative de l'activité ACP_1, la contribution des alloenzymes augmente dans l'ordre $p^a < p^b < p^c$ alors que pour l'effet de modulation des purines, la contribution des alloenzymes peut être soit $p^c < p^a < p^b$ soit $p^b < p^a < p^c$.
ADA est une enzyme polymorphique qui catalyse la désamination d'adénosine en inosine. Sa synthèse est contrôlée par un locus autosomique avec deux allèles codominants ADA^1 et ADA^2. L'activité enzymatique diminue dans l'ordre $ADA^1 > ADA^2$. L'étude d'une interaction possible entre ACP_1 et ADA a été suggéré par l'observation du fait que l'adénosine ne manifeste pas d'effets appréciables sur l'activité ACP_1, alors que, au contraire, l'inosine est un activateur relativement puissant.
Des facteurs ethniques peuvent affecter la sévérité de l'ictère physiologique chez les nouveaux-nés compatibles à terme. En fait, l'incidence de l'ictère significatif cliniquement chez les nouveaux-nés compatibles dans le système ABO est beaucoup plus faible chez les noirs que chez les blancs. Puisque la fréquence des sujets BA portant ADA^2 est également beaucoup plus faible chez les noirs que chez les blancs, celà peut contribuer à la différence de l'incidence de l'ictère néonatal entre les deux groupes ethniques (tableau IV).
Il est vraisembable que la variabilité métabolique secondaire au polymorphisme enzymatique peut contribuer significativement à une modulation du métabolisme de la bilirubine pendant la phase critique d'adaptation à la vie extrautérine. Les enzymes du métabolisme des nucléotides puriniques (y compris ADA), ACP_1 et Flavoenzymes représentent un complexe polygénique qui influence les taux de bilirubine au cours des premiers jours de vie et vraisemblablement également d'autres variables développementales.

Mots-clés: Adénosine déaminase, ictère néonatal, phosphatases acide, polymorphisme enzymatique.

Acknowledgements: We wish to thank Prof. F. J. ROHLF for helpful discussion. This work was supported by GRANTS from M. P. I. (Forty per cent Found) and CNR (grant n° 87.01249.11)

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Received August 11, 1986. Revised February 13, 1989. Accepted February 16, 1989.

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