Thursday, July 16, 1981

Oral Presentations

Coagulation – XIII

Factor VIII, Carrier Detection, Antibody

08:00–09:30 h

Coagulation – XIV

Factor VIII, Treatment, Antibodies

09:45–11:00 h

Cinema 2

0580

08:00 h

CARRIER DETECTION IN HAEMOPHILIA A BY MEASUREMENT OF FACTOR VIII CLOTTING ANTIGEN (VIIICAg) AND FACTOR VIII RELATED ANTIGEN (VIIIRAg). I.R. Peake*, R.G. Newcombe+, B.L. Davies*, R.A. Furlong*, C.A. Ludlam‡ and A.L. Bloom*.
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In order to assess the value of measurement of VIIICAg in the detection of carriers of haemophilia A, plasma samples were obtained on three separate occasions from each of 23 obligate carriers of mild and severe haemophilia, and 26 normal females. At each visit each sample was divided into three and each aliquot was then assayed for VIIICAg (immunoradiometric assay), clotting factor VIII (VIIIC) (two stage assay) and VIIIRAg (Laurell immunoelectrophoresis). After calculating median values at each visit, and for the three visits, a comparison of the ratios VIIIC/VIIIRAg and VIIICAg/VIIIRAg was made. Likelihood ratios (of being a carrier) were calculated using an unequal variance predictive method for both ratios. These showed that laboratory data calculated on the median of the three-visit medians had greater discriminatory power than a single-visit median value. Using the median of three visits both VIIIC/VIIIRAg and VIIICAg/VIIIRAg gave the same proportional misclassification of carriers as normals (4 of 23- 17%). However the ratios VIIICAg/VIIIRAg were more discriminatory due to the greater reproducibility between v isits of VIIICAg results than those of VIIIC. There was no statistically significant difference between VIIICAg/VIIIRAg (or VIIIC/VIIIRAg) ratios obtained from carriers of mild or severe haemophilia. The ratio VIIICAg/VIIIRAg was therefore shown to be the method of choice for carrier detection except theoretically in the rare CRM+ families.

0581

08:15 h

CARRIER DETECTION IN HEMOPHILIA "A" USING DISCRIMINANT ANALYSIS: A 5 YEAR STUDY. J.B. Graham, E.S. Barrow, H.M. Reisner. Department of Pathology and Curriculum in Genetics. University of North Carolina, Chapel Hill, NC, USA.

We counseled 174 possible or obligatory carriers of hemophilia "A" between January 1975-January 1980. Pedigree information provided a pedigree probability, πc, and blood samples the likelihood ratio favoring carriership (L.R.). The latter was arrived at from 2 bioassays of F. VIII activity (VIII:C & VIIIR:Ag) by linear discriminant analysis. Each consultand received counsel based on a final probability, P(C), produced by combining πc and L.R. Eighty % of the values of P(C) were either very high or very low which meant that clear-cut advice could usually be given. There were 29 obligatory carriers, 16 mothers of sporadic hemophiliacs, 73 sisters of hemophiliacs, and 56 more distant relatives. The individual values of P(C) could be used within each subset of carriers to relate mendelian expectation and observation. There were very few low P(C)s among mothers of sporadics suggesting that almost all were carriers. As a result, we now consider 0.8 to be a conservative πc for mothers of sporadics. Four women with low P(C)s were present among 29 obligatory carriers. This provided an estimate of negative diagnostic error (4/29=14%) and probably represented the effects of "lyonization". The observed:expected ratios of high:low P(C)s were normal among sisters of hemophiliacs and second and third degree relatives. Ten % of our consultands were pregnant when first seen. Twelve mothers with low P(C)s produced 11 liveborn, non-hemophilic children, 7 girls and 4 boys. Four with high P(C)s requested amniocentesis; 3 males were discovered and 2 were aborted. Five possible carriers with high P(C)s who had been seen before pregnancy, returned for assistance after becoming pregnant. All 5 requested amniocentesis, and fetoscopy if a male were present, and 4 males were fetoscoped. Two diagnosed as non-hemophilic in utero proved to be normal after delivery. A third could not be diagnosed, but was non-hemophilic at birth. The fourth, a hemophiliac, did not survive the procedure.

0582

08:30 h

CARRIER DETECTION of HAEMOPHILIA A in PREGNANCY by MEASUREMENT of FACTOR VIIIC/RAg and VIIICAg/RAg RATIOS

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The 1977 WHO Memorandum on carrier detection highlighted the need to test the methods in pregnancy, when plasma modalities of facor VIII are augmented. At KCH blood was taken into citrate from 21 pregnant obligate carriers of severe haemophilia A and 28 pregnant women from unaffected families, matched for age and period of gestation. The women, who were basal after a night's rest, were tested prior to prenatal diagnosis of haemophilia or other conditions, or to undergoing termination of pregnancy for unrelated causes.

One-stage factor VIIIC assays were done immediately; VIIIRAg (Laurell) after -40°C storage within 6 days; and VIIICAg immunoradiometrically in Cardiff on the remainder after varying intervals. Careful standardization was ensured between both laboratories.

At 17-22 weeks, VIIIRAg was elevated both in pregnant controls & carriers; VIIIC & VIIICAg levels were also raised, though less, in the controls (values in units/dl):

		VIIIRAg	VIIIC	VIIICAg	VIIIC/RAg	VIIICAg/RAg
CONTROLS						
(n 28)	$\bar{x}$	151	131	139	0.89	0.96
	s.d.	43	25	53	0.13	0.34
CARRIERS						
(n 21)	$\bar{x}$	146	60*	69*	0.42	0.47
	s.d.	41	24	57	0.14	0.29

*In pregnant carriers, VIIIC & VIIICAg are both lower than VIIIRAg ($p<0.001$). Likelihood ratios of carrier probability were plotted by the unequal variances predictive method: VIIIC/RAg discriminated much better between carriers & controls than VIIICAg/RAg, due to the wider spread of VIIICAg in each group, and unlike the findings in a related study of non-pregnant haemophilia A carriers.