SERUM IGM-GLOBULIN IN MALAYSIAN NORMAL AND DEFECTIVE INFANTS

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SUMMARY

The IgM-globulin levels were determined for 5,167 cord-sera of apparently normal infants and 281 sera of defective infants aged 4 months and younger. The significant level for IgM-globulin in neonates was found to be 20 mgm/dl (2 S.D. above mean of the normal) above which the level was regarded as abnormally raised.

Significant levels of IgM-globulin were found in 0.2% (11/5, 167) of normal neonates and in 40.6% (114/281) of defective infants which is more than 200 times the normal value. Combining the normal and abnormal rates, an overall figure of 23 intrauterine infections per 1,000 live births were obtained for Malaysia.

The advantages and disadvantages of the use of serum IgM-globulin elevations for the diagnosis of intrauterine infections were discussed.

INTRODUCTION

Of the five classes of human immunoglobulin, IgM-globulin is usually the earliest antibody to respond to a primary immune stimulus and since it is usually short-lived (lasting for about 6 months), its presence indicates recent infection. This immunoglobulin is essentially confined to the blood-stream where it plays an important protective role against infection.

Normally, IgM-globulin is not present or present in low concentration in the cord-sera of infants. As the maternal IgM-globulin is too large a molecule to cross the placenta, an elevated level of IgM-globulin in a newborn is a general indication of intrauterine infection whether with viral, bacterial, spirochaetal, protozoal or helminthic agents.

Although a study on the level of IgM-globulin has been done on the sera of normal Malaysian neonates [1], none so far has been done for Malaysian infants with congenital malformations. It was considered appropriate, therefore, to test for IgM-globulin the sera of infants, 4 months of age and younger, with defects indicative of the commonly recognized congenital infections viz. toxoplasmosis, rubella, cytomegalovirus infection, herpes simplex and syphilis or the "Torches" diseases (Table I) and to compare the results with those in normal cord-sera. This would assist in defining the proportion of congenital abnormalities due to intrauterine infection as opposed to those due to a host of other factors viz. single gene defects, chromosome anomalies, teratogenic drugs, ionizing radiation, enzyme defects, malnutrition, *in-utero* postural factors and others.

MATERIALS AND METHODS

Sera

Altogether, 5,167 cord-sera from infants of various races born in the Chinese Maternity Hospital, Kuala Lumpur were examined. In comparison, 281 sera of defective children, 4 months of age and younger, suspected of suffering from one of the "Torches" diseases (Table I) were

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TABLE I
CLINICAL FEATURES IN CHILDREN INFECTED WITH "TORCHES" DISEASES

System involved	Toxoplasmosis	Rubella	Cytomegalovirus infection	Herpes Simplex	Syphilis
Eye	Chorioretinitis Microphthalmia Ocular deviations	Cataract Chorioretinitis Microphthalmia	Chorioretinitis	Chorioretinitis Microphthalmia	Interstitial Keratitis Chorioretinitis } ± Optic atrophy }
Skin/Mucous membrane	Rash	Purpura	Purpura	Vesicular rash Mucosal haemorrhages	Vesicular, Bullous, Papulosquamous Rhagades Mucocutaneous
Ear		Deafness	Deafness		Deafness
CNS	Hydrocephaly Microcephaly Cerebral calcification Convulsions Encephalitis Mental retardation	Microcephaly Encephalitis Mental retardation	Microcephaly Hydrocephaly Microgyria Epilespsy Cerebral calcification Cerebral palsies Mental retardation	Convulsions Microcephaly Encephalitis Mental retardation	Tabes dorsalis Meningitis Pseudoparalysis Spasticity Speech defect Mental retardation
Cardiac		Patent Ductus Pulmonary stenosis Myocarditis		Dyspnoea	
Respiratory	Pneumonitis	Pneumonitis Pneumonia			
Liver	Enlarged Jaundice Hepatitis	Enlarged Jaundice Hepatitis	Enlarged Jaundice Hepatitis	Jaundice	Enlarged
Spleen	Enlarged	Enlarged	Enlarged		Enlarged

tested. The latter group of sera was obtained from various paediatric units in hospitals throughout the country. A much higher number of normal sera over abnormal sera had to be tested because of the very low rate of significant IgM-globulin levels in the normal sera.

Method

The Behring Tripartigen radial immunodiffusion plates were used to estimate IgM and IgA globulin. Sera with high IgA globulin value were regarded as being contaminated with maternal sera and therefore excluded.

RESULTS

Table II summarizes the results of IgM-globulin levels in the sera tested. The cord-sera mean IgM-globulin level in mgm/dl was 10.00 ± with a range of 5 to 22 mgm/dl. Of the defective children, the mean IgM-globulin in those less than 1 week old was 56.30 ± 51 (range: 7-200); in those 1 to 3 weeks old, 69.4 ± 59 (range: 7-198); and in those 1 to 4 months old, 72.9 ± 49 (range: 7-187). The overall mean IgM-globulin level in defective sera was 67.9 mgm/dl ± 51 (range: 7-200).

If the value of greater than 2 standard deviations (S.D.) from the mean of the normal cord-serum levels be considered as abnormally elevated, then from these figures 20 mgm/dl and above may be regarded as indicative of intrauterine infection. Thus, it may be noted that defective neonates less than 1 week old had a prevalence rate of 36.2 percent which is more than 180 times that of normal neonates which was 0.2 percent. Using 36.2% as an approximate estimate of the rate of intrauterine infection in infants it may be worked out that the significant IgM-globulin level for infants 1 to 3 weeks old could also be taken as 20 mgm/dl because at this level the infection rate for this group of infants (36.5 percent) was very similar to that of the younger infants (36.2 percent). However, for the older infants, aged 1 to 4 months

TABLE II
SERUM IgM LEVELS OF NORMAL AND DEFECTIVE MALAYSIAN CHILDREN

Group		SERUM IgM LEVELS (mgm/dl)				Total	Mean ± SD (range)
		Negative * (%)	5 - 19 (%)	20 - 49 (%)	50 & above (%)		
Normal (Cord-serum)		4,981 (96.4)	175 (3.4)	11 (0.2)	0	5,167	10.00 ± 4 (5-22)
DEFECTIVES	< 1 week old	48 (51.1)	12(15.5)	14 (14.9)	20 (21.3)	94	56.3 ± 51 (7-200)
				34 (36.2)			
	1 week - 3 weeks old	29 (60.0)	4 (7.8)	8 (15.4)	11 (21.2)	52	69.4 ± 59 (7-198)
				19 (36.5)			
	1 month - 4 months old	34 (25.2)	11 (8.1)	29 (21.5)	61 (45.2)	135	72.9 ± 49 (7-187)
				90 (66.7)			

* None or minimal

old, the significant IgM level had to be raised to 50 mgm/dl, as the rate at this level (45.2 percent) was comparable with 36.2 percent ($P > .05$) On the other hand, if 20 mgm/dl were considered to be the significant level for this age group the rate of 66.7 percent would be very much higher ($P < .0005$) than the estimated infection rate of 36.2 percent.

Totalling the figures for the three age-groups of infants (based on their respective significant IgM-globulin levels) we obtained an intrauterine infection rate of 40.6% (114/281) for defective infants. This, combined with the normal rate of 0.2% (11/5,167) gave an overall rate of 2.3% (125/5, 448) or 23 intrauterine infections per 1,000 live births for Malaysia.

DISCUSSION

The term "congenital malformation" is a collective one for many heterogeneous structural anomalies present at birth. About 2 percent of all babies are estimated to be born with serious congenital defects which form a major cause of perinatal and infant death or crippling disease if the infant survives. [2] However, marked differences in the incidence of minor defects have been observed in various centres and may vary from 3 percent [3] to 15 percent. [4] These figures are exclusive of congenital abnormalities present in stillborns and aborted foetuses. Nelson and Forfer [3] detected in 172 stillborn infants 31.5 percent with congenital abnormalities. Stevenson [5] discovered more than half of aborted foetuses to be grossly abnormal and embryos 3 to 10 weeks old were found to have more malformations than foetuses at the end of pregnancy. [6]

What proportion of all these congenital malformations can be attributed to intrauterine infection is not known in general. As this proportion is expected to vary with different countries depending on multiple factors like the different prevalence of the infections, host susceptibility, environmental and social conditions, each country has to determine its own incidence of intrauterine infections.

One method of achieving this is by examining the cord-sera of defective neonates for IgM-globulin. [7,12] Because the significant IgM-globulin level above which the results are considered abnormal is calculated from findings obtained with normal sera, the study population should include normal infants as well.

The use of serum IgM-globulin elevations for diagnostic purposes has both advantages and disadvantages. Because the test is non-specific, the levels can become increased with a variety of intrauterine infections, many of which may not be of clinical importance. On the other hand, it may be valuable in determining the role not only of infections of known importance but also of other infections in intrauterine illness. Sometimes infants infected *in utero* may appear normal at birth but develop symptoms later. For such cases screening for IgM-globulin serves to detect congenitally acquired infections early especially in mild forms of congenital disease. IgM-globulin elevations in cord-sera have been found to occur in inapparent as well as apparent maternal illness [8] and therefore may

help in giving a truer incidence of intrauterine infections in retrospective studies.

In this study, the percentage of raised IgM-globulin in normal neonates was extremely low (0.2%) probably because the neonates were from the urban centre of Kuala Lumpur. So far, no survey of this nature has been done in neonates from a rural population in Malaysia. In Tunisia, [9] of 412 normal neonates, 33.2 percent had IgM-globulin levels of 20 mgm/dl and above. In Latin America [10] raised IgM-globulin was found in 6.3 percent of urban middle-class population and 48.7 percent of rural population. In the U.S.A. [11] out of 2,600 neonates of Negro and Caucasian origin, 15 percent had IgM levels of 20 mgm/dl and above. The mean value in Malaysian neonates was 10 mgm/dl ± 4 which was low compared with that of Tunisia which was 16.5 mgm/dl ± 12.

Serum IgM-globulin levels have been related to birthweight. [14] In Tanzania IgM-globulin above 20 mgm/dl was found in 14 percent of full-term infants with normal weight, in 25 percent of preterm infants and in 40 percent of small-for-date infants.

Specific studies on the five "Torches" congenital diseases are currently being undertaken.

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