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Orthopaedic Clinic, University of Athens and Orthopaedic Department, Children's Hospital, Lemessou 41, Athens, Greece.

VIRAL ANTIBODY TITERS TO RUBELLA IN COXA PLANA OR PERTHES' DISEASE

Perthes' Disease: Is it the Late Osseous Residua of a Minor Prenatal Rubella?

JOHN A. MATSOUKAS

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Coxa plana (CP) still remains as much of an etiologic enigma as when it was first recognized as a clinical entity in the classic descriptions of Legg, Perthes and Calvé in 1910. Among all osteochondroses, CP is undoubtedly the one which is of most interest and has been most studied. The frequency of bilateral involvement also suggests a constitutional abnormality (Sharrard 1971).

Among the many suggested etiological agents are: trauma, infection, endocrine inbalance, metabolic disturbance, and heredity. Each of these theoretical possibilities has had its champion at one time or another, but none has received general acceptance. Figures suggest an incidence in the general population of about 1 per 2000 living. All surveys report a preponderance of males, the ratio being 4 or 5 males to 1 female. CP is unknown in Negroes. It has been said that trauma may be a precipitating cause. The least genetic reports are compatible with multifactorial inheritance (Wynne-Davies 1973). Also, the pathogenesis of CP is undetermined. Recent experiments support the vascular concept. Some authors believe that venous thrombosis is a more likely cause of CP than arterial occlusion. Another field of research has been the investigation of the child as a whole, rather than his hip in particular (Catterall 1971). It has been known for some years that these children are smaller, weigh less at birth, and have delayed bone age (Girdany & Osman 1968). I believe that CP reflects an unsettled generalized disturbance of congenital origin, rather than a localized disorder of the hip. For this reason I have been studying this "disease" from a completely different viewpoint. It is emphasized that the results of the present study support my hypothesis.

MATERIALS, METHODS AND RESULTS

The present study is subdivided into three parts. The first part includes the research for associated defects in a series of 60 children with CP. The second part is connected with research of the pattern of rubella response in 10 pairs of mothers and their affected children. Finally, the third part is related to the histologic study of vascular branches of five affected hips.

Part I

A careful survey for associated defects revealed the following (Table 1). When examined, in a series of 60 children with CP disease, two of them had epilepsy; one patient had congenital cardiovascular defect. Inguinal hernia was present in ten children, of whom one had a severe speech defect, one renal disease and one hypospadias. Minor skeletal defects such as spina bifida occulta were present in 17 children, dental abnormalities in five and dermatoglyphic alterations in three. Two children also had hypacusia of unknown origin.

Table 1. The various associated defects found in 60 children with coxa plana.

No.	Associated defect(s)	No. of cases
1.	Epilepsy	2
2.	Patent ductus arteriosus	1
3.	Renal disease (calcinosis)	1
4.	Inguinal hernia	10
5.	Hypospadias	1
6.	Speech defect	1
7.	Spina bifida occulta	17
8.	Dental anomalies	5
9.	Dermatoglyphic alterations	3
10.	Hypacusia	2

Part II. Testing for rubella

1. Viral antibody titers were determined by hemagglutination inhibition techniques in microtiter plates. Rubella titers were performed acording to the method that no patient has a positive history of natural rubella infection nor was vaccinated by live rubella virus vaccine. To be able to compare the results we have used two control groups, one of 10 non-affected children and one consisting of their mothers. All the controls were approximately of the same age and came from the same geographic areas.

1. Viral antibody titers were determined by hemagglutination inhibition techniques in microtiter plates. Rubella titers were performed according to the method of Stewart. Sera were treated with kaolin, adsorbed with erythrocytes from 1-day-old chickens, and heat inactivated at 56° C for 30 minutes prior to testing against four hemagglutination units of rubella virus strain M - 33. Two-fold dilutions of

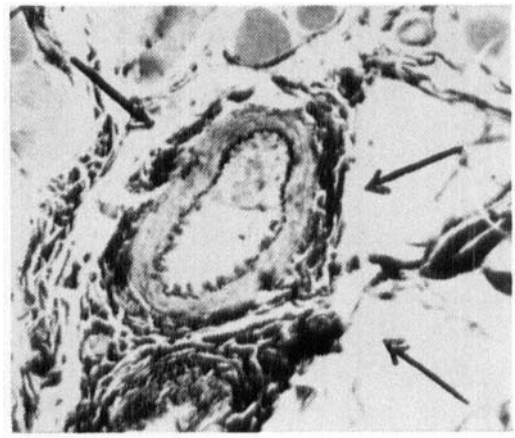

Figure 1. Small artery from the articular vessels of a child with coxa plana. Attention is drawn to the eccentric endothelial thickening and to the increase in wall-to-lumen ratio (Verhoeff's elastic stain. × 250).

serum were used beginning with ¼ dilution, and viral antibody titers were expressed as the reciprocal of the highest dilution which completely inhibited hemagglutination of the chicken erythrocytes. Analysis of positive sera indicated that (a) persistent rubella HI antibody titers among tested children with CP have been found only in the younger affected children. They were much lower than titers seen among those of the same age with postnatally acquired rubella. (b) Negative sera correspond to those of control children except for two where there was evidence of a four-fold rise in rubella antibody titer, that was indicative of a recent infection. (c) HI antibodies persist to detectable levels in all mothers of the affected children. Such levels were suggestive of the likelihood that only some years had passed since the probable rubella attack. Although neutralizing and HI antibodies persist for life, in the majority of the control mothers positive results

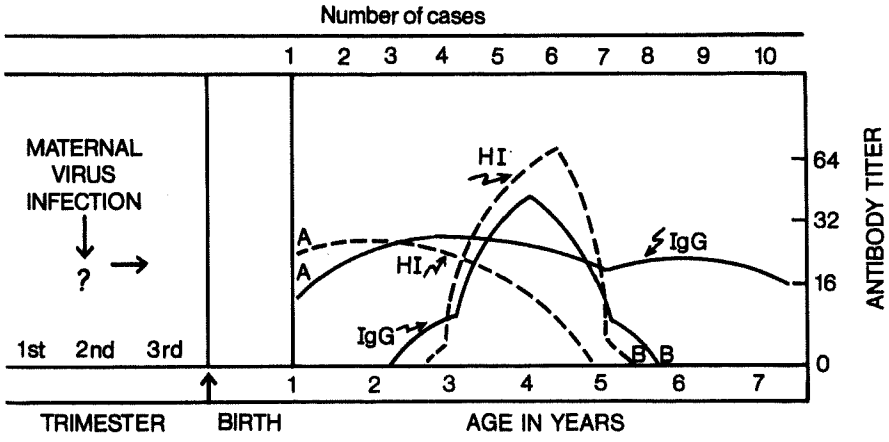

Figure 2. Diagram illustrating the pattern of antibody response in the two groups of children. A: affected; B: controls.

were not obtained. Only three controls had positive sera, but the geometric mean titers of these were much lower than those of the test mothers.

2. Neutralizing antibodies, particularly IgG (7S) persist in all the test children and the same antibodies persist to detectable levels in all the test mothers. This pattern was in marked contrast to the pattern of both control groups. Actively acquired IgG appears to be the dominant rubella antibody in all affected children. Among the controls higher levels of antibody were found in only two. Half of the control mothers were negative whereas the other half showed minimal levels of IgG.

In conclusion, the pattern of antibody response of the patients and their mothers differs significantly from the pattern of the controls. The main difference lies in the higher levels of antibodies in all the affected children and in all their mothers.

Part III. Histologic study

Vascular lesions were studied in five children with CP in connection with surgical intervention. The vulnerable vascular channels are the cervical branches arising from the cervical circle and which traverse the joint cavity to reach the capital femoral epiphysis. Several such cervical branches have been examined. The severity of involvement varied. No significant lesions were found in arterioles or veins. Diffuse proliferation of the arterial intima was the most characteristic lesion in all these cases. At some sites the intima was more than twice as thick as the remaining arterial wall. The internal elastic lamella and media were almost always unchanged, even in the presence of a greatly thickened intima (Figure 1). Conclusion: The characteristic finding was intimal fibromuscular proliferation.

DISCUSSION

The surprising findings of the present study provide some support for the suggestion that CP probably reflects the effect of rubella virus during the prenatal period. It is well known that the multiplicity of defects is the striking feature of congenital rubella in children.

Virtually every organ may be involved; singly, multiply, transiently, or progressively and permanently (Krugman & Ward 1973). It is true also that rubella infections after the 14th week of pregnancy do not result in malformation, but they do endanger the fetus to some extent. Overall, manifestations were less severe and more subtle than those of infections during the first trimester (Warkany 1971). Developmental delay was seen in young affected children (Cooper 1968). Renal and ureteric malformations were noted by Gregg (1941) and other workers. Hypospadias has been observed repeatedly in boys with congenital rubella. There was reports in the past of spina bifida, renal anomalies and hypospadias following maternal rubella that were usually considered coincidental. An increased incidence of indirect inguinal hernias has been reported (Hardy & Sever 1968). Roentgenography of

the long bones of a considerable number of children with congenital rubella shows irregular mineralization at the areas of ossification and in the metaphyses (Singleton et al. 1966). Unusual dermatoglyphics associated with the congenital rubella syndrome were described by Achs & Siegel in 1966. Among Negro women, the absence of neutralizing antibody was significantly greater than among whites (Sever 1964). The fibromuscular changes in our patients' vessels conform to those described in children with congenital rubella. Rubella is notorious for the production of proliferative vascular lesions (Esterly & Oppenheimer 1967). If there really is an etiologic relationship then the production of an unsuspicious vasculo-osseous syndrome is explained. It is still possible to account fully for the clinical features of CP on the basis of a vasculitis and a biologically inferior bone. This vasculopathy which is a constant feature in all the cases examined may cause one of infarction necrosis. In addition, a well documented arterial communication between the upper and lower cervical circulation in the female can be the explanation of the differences of incidence of CP in the two sexes.

To summarize, all the above data, viz. clinical, histological and particularly immunological aspects, indicate the need for a discussion of a probable etiologic correlation between prenatal rubella and CP. Despite absence of lesions classically associated with rubella syndrome this osseous disorder may represent a forme fruste of that disease. It is very likely that CP is not a localized disorder nor a distinct entity but the late osseous residua or stigma of very mild prenatal viral infection with a sub-clinical course in the mother. If that is true, a progressive disappearance of CP is possible in the future.

SUMMARY

The present study seriously raises the question as to whether coxa plana is etiologically connected to the rubella virus. Some findings suggests a probable causal correlation between prenatal rubella and coxa plana. A regional vasculitis in association with biologically inferior bone probably constitutes the fundamental pathogenetic mechanism of this condition. However, this matter is still awaiting elucidation.

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Correspondence to:

John A. Matsoukas, M.D.
Orthopaedic Surgeon
Vassilissis Sofias 124 A
Athens–609, Greece