Persistence of "Australia Antigenemia" in Mentally Retarded Children Seven Years After Virus Hepatitis

Hajime Hayashi
Gerald A. LoGrippo
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Hajime Hayashi, Ph.D.* and Gerald A. LoGrippo, M.D.*

Australia antigen and antibody were assayed in acute and convalescent (1, 4 and 6 months) phase sera from 80 children with infectious hepatitis in an institution for the mentally retarded. A higher incidence of Australia antigenemia was found in 18 of 40 (45%) mongoloid children as compared to 9 of 40 (23%) non-mongoloid children. Australia antigen persisted 7 years after the hepatitis epidemic in 11 mongoloid and 2 non-mongoloid children with hepatitis. None of the hepatitis group, with or without Australia antigenemia, demonstrated precipitable antibody to the Australia antigen. The discussion emphasizes the lack of virologic and immunologic evidence relative to: (1) the specific association of Australia antigenemia to virus hepatitis of the serum variety, (2) the persistence of Australia antigenemia in mongoloids associated with transaminase elevations, and (3) the specificity of Australia antigenemia to the hepatitis virus particle and/or protein.

Although the properties of the Australia antigen are yet to be adequately characterized, it is being hypothesized that the antigen is closely associated with virus hepatitis,^—^ and is a specific virus antigen of the serum hepatitis (SH) strain(s).^—^ The frequency of Australia antigenemia is reported in individuals with SH,^—^ infectious hepatitis (IH),^—^ mongolism,^—^ and certain clinical entities,^—^ as well as the normal population.^

In this report, the frequency and persistence of the Australia antigenemia were re-evaluated 7 years after the initial epidemic in 80 mentally retarded children in a 1962 institutional outbreak of virus hepatitis. In addition, three other biochemical tests compared in this report with the Australia antigen and antibody are: immunoglobulin-M (IgM), serum transaminase levels (SGPT and/or SGOT) and C-reactive protein (CRP).

Materials and Methods

Clinical patients. Eighty of 652 mentally retarded institutionalized* children (1-15 years of age in 1962) had clini-
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cal signs and symptoms of virus hepatitis associated with jaundice, elevated serum transaminase levels and elevated serum immunoglobulin values (Igs; IgM, IgG and IgA). The hepatitis-affected patients were in a relatively new institution. The outbreak was the institution’s first epidemic and was classified as IH on the basis of its short incubation period, the parenteral route of infection and the abrupt nature of the epidemic.

Serum specimens were collected during the acute phase of hepatitis and at one, three to four and six to seven months after the clinical onset. Serum Ig levels and SGPT values were assayed in 1962 in the relatively fresh state and reported elsewhere. However, the Australia antigen and antibody assays as well as CRP were performed on these sera in 1969 from frozen stored (—20 C) specimens. In 1969, fresh sera were collected from 42 of the 80 inmates for re-evaluation and all determinations were made on fresh, unfrozen specimens.

Determination of serum proteins and enzyme. An immuno-chemical method of analysis is used for determining serum proteins (Igs, CRP, Australia antigen and antibody). It is a quantitative micro-double diffusion in agar-slide technic employing a five-hole, plastic-template instead of making holes in agar. By this technic, Igs and CRP values are determined in milligram per 100 ml of serum. The normal values established for this laboratory are: IgM (30-120 mg/100 ml); and CRP-Negative (less than non-detectable quantities). The Australia antigen and antibody are also determined by the same immuno-diffusion technic using a seven-hole, plastic template. All precipitation bands are identified with known antigen and antibody reactants. It is important to emphasize that hemophiliac and hepatitis patients carry a variety of precipitable reactants other than the Australia antigen and antibody in their sera. These reactants must be differentiated by specific Australia antigen and antibody. Serum transaminase (SGPT and/or SGOT) are performed on fresh serum by a clinical biochemistry laboratory; normal values are less than 40 units per ml.

Results

Since a high incidence of Australia antigenemia was found in stored, frozen sera from children with hepatitis among institutional mongoloids, re-evaluation of the data became necessary with fresh sera from those individuals. In addition, Australia antigen positive tests warranted re-evaluation for comparative study with other biochemical tests associated with virus hepatitis.

Table I gives the number and percentage of Australia antigen positive serum in children with virus hepatitis in 1962; 40 were mongoloids (Down’s syndrome) and 40 nonmongoloids (other mentally retarded children). The Australia antigen was positive during the icteric stage in 18 of 40 (45%) mongoloids and 9 of the 40 (23%) nonmongoloids. The higher average incidence of Australia antigenemia in these children (34%) is influenced by the number of mongoloids in this epidemic (45% in mongoloids and 23% in the other children). No specific precipitable antibody to Australia antigen
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Table I

AUSTRALIA ANTIGEN AND ANTIBODY IN INFECTIOUS HEPATITIS

<table>
<thead>
<tr>
<th>Clinical Entities</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Down's Syndrome</td>
<td>40</td>
</tr>
<tr>
<td>Others</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
</tr>
</tbody>
</table>

* Australia antigen (Au-Ag) and Australia antibody (Au-Ab).

** Australia antibody was negative during 2-6 months convalescence.

was detected in any of these children during the six months’ convalescent study.

Table II gives the number of children re-evaluated in 1969 and shows the number of mongoloids and non-mongoloids persisting with Australia antigenemia seven years after hepatitis. In 1969, only 42 of the 80 children (23 mongoloids and 19 nonmongoloids) were available for study. In 12 of 23 mongoloids who were positive for Australia antigen in 1962, 11 of these persisted with Australia antigenemia in 1969. In addition, five other mongoloids with hepatitis (who were negative with Australia antigen in 1962) became positive by 1969.

Among 19 nonmongoloid children with hepatitis, five of these were positive for Australia antigen in 1962 but only two persisted with detectable antigenemia in 1969. In addition, two of the nonmongoloid children with hepatitis in 1962, who were Australia antigen negative during six months’ follow-up, were found to be positive in 1969.

In Table III, Australia antigenemia is compared with three serum biochemical changes associated with acute stages of virus hepatitis: SGPT, IgM and CRP. In the 80 children studied, SGPT values are most consistently elevated, IgM elevation is next, followed by CRP and Australia antigenemia. The Australia antigenemia was not de-
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Table II

PERSISTENCE OF AUSTRALIA ANTIGENEMIA
7 YEARS AFTER HEPATITIS EPIDEMIC

<table>
<thead>
<tr>
<th>Clinical Entities</th>
<th>Total</th>
<th>Australia Antigenemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down's Syndrome</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Others</td>
<td>19</td>
<td>5</td>
</tr>
</tbody>
</table>

* Seven patients with hepatitis in 1962 were negative to Australia antigen for 1 - 4 and 6 months post hepatitis. However, these became Australia antigen positive during the interval indicated.

Table III

AUSTRALIA ANTIGENEMIA AND OTHER SERUM TESTS
IN INFECTIOUS HEPATITIS

<table>
<thead>
<tr>
<th>Number of Icteric Patients</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>(% positive)</td>
</tr>
</tbody>
</table>

* Serum glutamic pyruvic transaminase (SGPT), immunoglobulin-M (IgM), C-reactive protein (CRP) and Australia antigen (Au-Ag). (+) or (†) signs indicate serum values above normal levels.
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tectable in 66% of the children during the acute stage of virus hepatitis, thus indicating Australia antigenemia to be the least sensitive test of the four studied. Table IV shows further analysis of these tests. There is lack of correlation among IgM, CRP and Australia antigenemia during the acute and six months' convalescent study, with percentages varying considerably. This is true whether the tests are compared individually or in combinations, as shown. These tests appear to reflect the host's responses to nonspecific inflammatory conditions.

Discussion

The literature emphasizes the association of Australia antigenemia with serum hepatitis (SH) of the long incubation form of virus hepatitis (41-108 days). Our data support the association of Australia antigenemia with infectious hepatitis (IH) of the short incubation form (less than 40 days). In our study, the institutional outbreak of virus hepatitis was of the IH variety, considering the clinical aspects of the disease, short incubation period, parenteral route of infection and the abrupt onset and termination of the epidemic. Australia antigenemia was found in 27 of 80 inmates (34%) with clinical jaundice. In addition, serum transaminase (SGPT) and serum immunoglobulins (IgM and IgG) were also elevated above normal values. The epidemiologic and clinical features of the outbreak indicated the infectious variety of hepatitis. Although we could not classify the epidemic as moderately contagious, since 34% of the icteric cases demonstrated Australia anti-

Table IV

LACK OF CORRELATION BETWEEN AUSTRALIA ANTIGENEMIA AND HOST'S INFLAMMATORY RESPONSES IN INFECTIOUS HEPATITIS

<table>
<thead>
<tr>
<th>Tests Positive</th>
<th>Percent in 80 Children</th>
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<tbody>
<tr>
<td></td>
<td>Acute</td>
</tr>
<tr>
<td>None (Normal values)</td>
<td>19.5</td>
</tr>
<tr>
<td>IgM↑</td>
<td>CRP+</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM↑ , CRP+ , Au-Ag+</td>
<td>17.1</td>
</tr>
<tr>
<td>IgM↑ , CRP+ , Au-Ag+</td>
<td>1.2</td>
</tr>
<tr>
<td>IgM↑ , CRP+ , Au-Ag+</td>
<td>8.5</td>
</tr>
<tr>
<td>IgM↑ , CRP+ , Au-Ag+</td>
<td>15.9</td>
</tr>
</tbody>
</table>

* See footnote in Table III.
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genemia, we questioned whether our outbreak was IH or SH in nature. If IH and SH varieties were both present among patients, it would be difficult to explain in a relatively new institution the mixed hepatitis varieties present with abrupt onset and sudden termination in four to six weeks. Moreover, there has been no overt hepatitis in this institution since 1962. Whether Australia antigenemia is associated with the serum (long incubation) variety of hepatitis will remain unresolved until further immunologic and virologic evidence is obtained.

Sutnick et al. reported that in several large institutions the frequency of Australia antigenemia was high (27.7%) in patients with Down’s syndrome and low (3.3%) in patients without Down’s syndrome. They also reported that Australia antigen is associated with elevated SGPT values in Down’s syndrome. In our study, the higher incidence of Australia antigenemia (45%) was also found in children with Down’s syndrome. There was a lower incidence (23%) in the children with other abnormalities. In 1969, the incidence of Australia antigenemia among mongoloids (45%) during the acute stage of IH became even higher (70% from 45%). However, we do not know how many of these children may have had Australia antigenemia before the onset of hepatitis in 1962. In contrast to Sutnick et al., transaminase levels in our children with persisting Australia antigenemia were normal in 1969.

The literature emphasizes the specificity of the Australia antigen as a virus protein on a hypothetical basis. Shulman et al. reported low complement fixing antibody titers (1:5 or less) in a small percentage (3 of 22) of hepatitis patients, with no detectable antibody precipitable to Australia antigen. In our study with serial serum specimens at one, four and six months after acute hepatitis, none of the 27 children with Australia antigenemia converted to positive precipitable antibody. Moreover, Australia antibody of the precipitable type has not been demonstrated in 57 adult hepatitis patients with Australia antigenemia. There is need for more serological evidence of the specificity of this antigen to the etiological agent or agents because of the lack of sero-conversion to detectable precipitable antibody in hepatitis patients with Australia antigenemia and the small percentage of patients with low complement fixing antibody titers.

Based upon clinical criteria, serum or infectious varieties of virus hepatitis cannot be satisfactorily differentiated as to incubation period, route of infection or administration of blood and blood products. Both varieties are transmitted by parenteral and oral routes. As documented in the Willowbrook institution by Krugman and associates, incubation periods are suitable criteria when initial exposures are under investigational control. However, in clinical cases, the majority of patients are unclassified since blood and blood products may contain either variety. The incubation period and onset of clinical signs and symptoms often fall mid-zone (30-50 days) between the two varieties. Since our institutional and clinical studies with IH patients also demonstrate Australia antigenemia, the presence of this antigen is not
a reliable test for a differential diagnosis.

The conclusions being made in the literature warrant more serologic and virologic evidence relative to: (1) the specific association of Australia antigenemia to virus hepatitis of the serum variety;\(^4,6\) (2) the persistence of Australia antigenemia in mongoloids associated with transaminase elevations;\(^11\) and (3) the specificity of Australia antigenemia to the hepatitis virus particle and/or protein.\(^2,4,17-21\)

Acknowledgement

Grateful appreciation is expressed to the medical staff of the Plymouth State Home and Training School, Northville, Mich. for their cooperation in making the serum specimens available for this study.

REFERENCES


