Electrocardiographic Abnormalities in Epidemic Hepatitis

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Myocarditis has been reported in patients dying with viral hepatitis. With the increasing incidence of the disease, recognition of myocardial involvement is apparently important. The nature of the abnormalities suggested several factors including ischemia and local electrolyte disturbance of myocardium. The incidence of abnormalities was greater in the out-patients and in those with tachycardia, and greatest at the peak of the epidemic. Abnormalities showed no relation to the severity of the jaundice or of the illness or to the serum protein levels.

MYOCARDITIS not infrequently occurs in virus diseases such as anterior poliomyelitis, mumps, measles, varicella, infectious hepatitis, and primary pneumonia. The electrocardiogram may be the basis of diagnosing myocardial involvement in viral diseases because other manifestations are often absent or minor. Myocardial changes in epidemic viral hepatitis have been infrequently reported in the literature and there are few comprehensive studies of electrocardiographic changes with multiple lead records. The incidence of viral hepatitis appears to be on the increase and recognition of myocardial involvement may prevent cardiac catastrophies or residual changes by allowing sufficient convalescence. Therefore, when an epidemic of viral hepatitis occurred in Jaipur in 1955, the present investigation was undertaken to determine the incidence and the nature of the electrocardiographic abnormalities and their relation to various clinical and other factors.

Material and Methods

One hundred forty patients with jaundice due to epidemic hepatitis but without other cardiovascular disease were studied. Fifty-seven patients, of whom 10 were comatose, were admitted to the hospital; 83 attended the out-patient department. There were 127 males and 13 females with ages varying from 8 to 55 years. The duration of illness at the time of first observation varied from 1 day to 22 weeks. Electrocardiograms with standard leads, I, II, III, and unipolar leads, aVR, aVF, aVL, and V1 to V6 were recorded routinely and additional chest leads were taken in a few cases. Serial tracings were recorded in all in-patients and a large majority of the out-patients. In patients with hepatic coma tracings were often repeated twice a day. Sinus tachycardia or bradycardia by itself and minor changes in the amplitude of the QRS were not considered abnormal. Changes of P and T waves were considered as abnormalities only if they became normal on serial observations. A Q-T ratio of more than 1.09 in males and 1.08 in females was considered abnormally prolonged. Icterus index, total serum proteins, and serum albumin and globulin were determined and repeated, particularly when the electrocardiogram showed any abnormality.

Results

Electrocardiographic Findings

Definite abnormalities were confirmed by serial tracings in 61 cases and are summarized in table 1.

Rate and Rhythm. The cardiac rate was 90 or more in 23 cases, 60 or less in 28 cases, and 61 to 89 in 89 cases. The incidence of abnormal electrocardiograms in cases with tachycardia was nearly twice as high as those with bradycardia (table 2). Premature ventricular beats were seen in 2 cases and nodal rhythm in 1 case.

P Wave. Abnormal P waves were seen in 10 cases: they consisted of broad or tall P waves, more than 0.12 mm. wide or 3 mm. high in 6 cases, and inverted P in 4 cases. The abnormality was never isolated but always associated with some other abnormality in the electrocardiogram.

QRS Complex. Slight increase or diminution in the amplitude of QRS after recovery occurred with nearly equal frequency. A pattern of left ventricular hypertrophy was seen in 1
TABLE 1.—Summary of Electrocardiographic Abnormalities in Sixty-one Cases

<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>P changes</td>
<td>10</td>
</tr>
<tr>
<td>T changes</td>
<td>48</td>
</tr>
<tr>
<td>S-T segment depressed</td>
<td>24</td>
</tr>
<tr>
<td>Q-T interval prolonged</td>
<td>6</td>
</tr>
<tr>
<td>Conduction defects</td>
<td>3</td>
</tr>
<tr>
<td>Ventricular premature beats</td>
<td>2</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>1</td>
</tr>
<tr>
<td>Hypopotassemia</td>
<td>2</td>
</tr>
</tbody>
</table>

TABLE 2.—Incidence of Cases with Abnormal Electrocardiograms According to Cardiac Rate

<table>
<thead>
<tr>
<th>Cardiac rate</th>
<th>Total cases</th>
<th>No. with abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 or less</td>
<td>28</td>
<td>9 (32%)</td>
</tr>
<tr>
<td>90 or more</td>
<td>23</td>
<td>15 (65%)</td>
</tr>
<tr>
<td>61–89</td>
<td>89</td>
<td>37 (41%)</td>
</tr>
<tr>
<td>Total</td>
<td>140</td>
<td>61</td>
</tr>
</tbody>
</table>

case, and QRS duration of 0.13 second, suggesting intraventricular conduction defect, occurred in another.

S-T Segment and T Wave. Changes in the S-T segment and T wave were the most frequent abnormalities. S-T depression was seen in 24 cases and occurred most frequently in leads II, III, aV_{F} and V_{4-6}. Changes in T wave were seen in 48 cases and included tall T in 4 cases, low voltage or flat T in 29 cases, abnormal contour with broad or bifid summit in 7 cases, and inverted T in 35 cases. They occurred most frequently in leads II, III, aV_{L}, aV_{F}, and V_{1-2}. In 2 cases T waves were inverted in all the precordial leads.

T inversions were of different patterns: (1) "Coronary T-wave pattern" with pointed apex or terminal dipping of T in 9 cases; (2) inversion of initial segment with S-T depression but upright terminal T in 17 cases; (3) complete inversion of T with S-T depression of the "straight line type" in 7 cases; and (4) hammock-like depression of S-T segment with inverted T and elevated U wave suggesting a hypopotassemia pattern in 2 cases.

An interesting finding was isolated T-wave negativity in precordial leads in the topographic sense in that the flanking leads showed these changes to a much lesser extent or showed upright T waves. This was seen in 5 cases, in 3 cases in V_{3} only and in 1 case each in V_{1-4} and V_{5-6} (fig. 1). These changes were transient, the T wave becoming upright within 3 to 11 days. All the 5 patients were between 20 to 27 years of age and 3 of them were females, the possibility of coincident coronary artery disease being therefore very little. Q-T ratio increased in 2 and decreased in 3 of them by more than 0.06 when the electrocardiogram returned to normal, but it was not prolonged above normal limits in any of them. An exercise test, done after recovery in 2 cases, was negative.

U Wave. There was isolated inversion of U in lead V_{3} in 1 case (fig. 1).

Conduction Defects. These were seen in 3 cases. In 1 case the duration of QRS was 0.13 second, suggesting intraventricular defect. In another case the P-R interval was prolonged to 0.22 second, returning to normal later. The third case showed at various stages of the illness complete heart block, second degree heart block, and prolonged P-R interval of 0.38 second (fig. 2). Prolongation of P-R in this case has persisted up to the present nearly a year after recovery from the illness. During the illness in the hospital this patient had suddenly developed tachycardia, gallop rhythm, and a systolic murmur indicating onset of acute myocarditis.

Q-T Interval. The Q-T ratio was increased in 6 cases ranging from 1.14 to 1.35. Three of these cases were in hepatic coma of whom 2 died. The 2 fatal cases showed a pattern of hypopotassemia. One had jaundice for 16 weeks and was comatose for 48 hours prior to admission, and died within a few hours of the recording of the electrocardiogram, so that estimation of serum potassium could not be done. The second case had had jaundice for 20 weeks before admission when the first electrocardiogram recorded showed these changes (fig. 3). She became comatose 48 hours later and died on the eighth hospital day. Repeated estimation of serum potassium revealed normal values and administration of potassium chloride produced no significant alteration in the electrocardiogram.
Correlation of Electrocardiographic Abnormalities with Other Factors

Electrocardiograms were abnormal in 40 (48 per cent) of the 83 out-patients and 21 (37 per cent) of the 57 in-patients, the incidence of abnormalities being greater in the former even though the tracings were repeated less often and the severity of the illness was comparatively less in them than in the in-patients. It is likely that the greater activity of the out-patients who were often ambulatory may have produced a greater stress on the myocardium.

The incidence of cases with abnormalities according to the date of onset of illness was
Fig. 2. Various grades of heart block at different times in the same patient. A. Normal sinus rhythm with bradycardia. B. Complete heart block. C. Partial heart block with Wenckebach phenomenon. D. Prolonged P-R interval of 0.38 second.

Fig. 3. Depressed S-T segment, inverted T, prominent U, and prolonged Q-T, changes characteristic of hypopotassemia in a female patient who died later.

Table 3.—Incidence of Cases with Abnormal Electrocardiograms According to the Month of Onset of Disease

<table>
<thead>
<tr>
<th>Month</th>
<th>Total cases</th>
<th>No. with abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aug. 1955</td>
<td>3</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>Sept. 1955</td>
<td>16</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>Oct. 1955</td>
<td>19</td>
<td>5 (26%)</td>
</tr>
<tr>
<td>Nov. 1955</td>
<td>23</td>
<td>14 (61%)</td>
</tr>
<tr>
<td>Dec. 1955</td>
<td>30</td>
<td>20 (66%)</td>
</tr>
<tr>
<td>Jan. 1956</td>
<td>27</td>
<td>11 (40%)</td>
</tr>
<tr>
<td>Feb. 1956</td>
<td>11</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>March and April 1956</td>
<td>11</td>
<td>3 (27%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>140</strong></td>
<td><strong>61</strong></td>
</tr>
</tbody>
</table>

greatest at the height of the epidemic (table 3) and suggested some relationship to the epidemiology of the infection.

Incidence of abnormalities was not related to the severity of the jaundice as determined by the icterus index (table 4) nor was it related to the severity of the illness. For example, 4 of the 10 patients with hepatic coma had normal tracings. Myocardial involvement as suggested by abnormal electrocardiograms in the other 6 cases did not indicate a grave prognosis either, as 4 of them recovered.

Abnormal and normal electrocardiograms
were seen with equal frequency in cases with normal serum protein values as well as in those with diminished proteins and reversal of albumin-globulin ratio. Abnormalities appeared at any time from the first day to the twentieth week of the illness and were usually transitory in nature. In only 1 instance did the abnormality, a prolonged P-R interval, persist.

**DISCUSSION**

Isolation of the "encephalomyocarditis" virus\(^9\) \(^{10}\) from the myocardium of anthropoid apes who apparently died of myocarditis and of the poliomyelitis virus\(^11\) from the hearts of patients dying of this disease suggests the possibility that the virus may directly attack the myocardium in certain viral diseases. The derangement of myocardial function evidenced by electrocardiographic changes may, however, be due to elements other than specific myocarditis including extracardiac variables in the form of chemical, pharmacologic, thermal, and metabolic influences; alterations in the tone of extrinsic cardiac nerves; and the cardiac causes like pre-existing valvular disease or myocardial necrosis.

In epidemic hepatitis myocardial changes have been reported in the literature in the form of diffuse serous inflammation, foci of necrosis of isolated muscle fibers, changes in the bundle of His\(^6\), hemorrhages in the heart\(^2\), interstitial and perivascular cellular infiltration, parenchymal degeneration described as myocarditis,\(^12\) and hemorrhagic pericardial exudate.\(^5\) The electrocardiographic changes in hepatitis have been attributed to concentration of bile in the blood, changes in serum proteins, electrolyte disturbances, autonomic imbalance, myocardial anoxia, and specific virus myocarditis.\(^13\)

In the present investigation cardiac causes and pharmacologic and thermal influences were excluded. The abnormalities appeared to have some relation to the epidemiology of the infection, the activity of the patient, and the cardiac rate, but no relation to the severity of the jaundice, the severity of the illness, and the serum protein levels. The isolated negativity of T or U-wave seen in this series does not appear to have been reported previously in hepatitis. T negativity, limited to or about the lead V\(_4\), has been reported in healthy males.\(^14\) In all our cases the T waves became upright later. Schlant and co-workers\(^15\) suggested that isolated T negativity represented the clinical counterpart of an ischemic phase of myocardial infarction. It may occur in stress tests indicating a positive test of coronary insufficiency. Inversion of U wave has been found in coronary artery disease.\(^16\) These changes therefore suggested that ischemia of the myocardium was one of the factors responsible for electrocardiographic abnormalities.

Prolongation of the Q-T interval in viral hepatitis has been interpreted as insufficiency of cardiac energy\(^17\) and disturbance of cardiac metabolism with diffuse myocardial involvement.\(^18\) Of the 6 cases with this abnormality in this series 3 were in hepatic coma. Two of these comatose patients also showed other severe abnormalities, suggesting the pattern of hypopotassemia, and died. Four patients, however, recovered without any residual changes. According to Lyon\(^19\) the prolonged Q-T is not found in the early icteric stage of the disease but takes some time to develop and is then found in less severe cases. In the present series it was seen as early as the fourth day of the illness and with an icterus index as high as 150.

Occurrence of various grades of heart block during the illness in 1 case was suggestive of lesions in the bundle of His described by Saphir and co-workers;\(^6\) persistence of the prolonged P-R interval in this case indicated permanent isolated damage in the bundle. That the electrolyte disturbance may be local in the myocardium and not be present in the blood was indicated by the normal values of serum potassium in 1 of the 2 cases with changes characteristic of hypopotassemia in which these determinations were made.

Recently, Saphir and co-workers\(^6\) found

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**Table 4.—Incidence of Cases with Abnormal Electrocardiogram According to Icterus Index**

<table>
<thead>
<tr>
<th>Icterus index</th>
<th>Percentage of cases with abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-25</td>
<td>40</td>
</tr>
<tr>
<td>26-50</td>
<td>60</td>
</tr>
<tr>
<td>51-100</td>
<td>46</td>
</tr>
<tr>
<td>above 100</td>
<td>50</td>
</tr>
</tbody>
</table>
Acute myocarditis in 4 of the 6 patients dying with viral hepatitis and recommended electrocardiographic studies in every patient with hepatitis. The present study showed a high incidence of abnormalities and their nature suggested that myocardial ischemia, diffuse disturbance of myocardial metabolism, lesions of the bundle of His, and local electrolyte disturbance in the myocardium were some of the factors contributing to the abnormalities.

It is, however, difficult to evaluate the significance of the myocardial involvement demonstrated by these abnormalities. In spite of their high incidence there was only a single instance of a residual abnormality, in the form of prolonged P-R interval. This patient was an in-patient who had proper bed rest and treatment at the time of the acute myocarditis, and the heart block persisted despite a prolonged convalescence. Again 6 of the 10 patients in hepatic coma showed abnormalities but only 2 died; they showed the most severe changes of a hypopotassemic pattern and had a prolonged illness of more than 4 months. These 2 were the only fatal cases in the entire series. To what extent the myocardial involvement contributed to the death of these 2 patients is difficult to estimate, especially because unfortunately necropsy could not be obtained. It seems possible, however, that at least in 1 of them in whom the serum potassium was determined and was normal, the death was due to local electrolyte disturbance and severe myocardial damage.

Summary

One hundred forty patients with jaundice due to epidemic hepatitis were studied to determine the incidence and the nature of the electrocardiographic abnormalities and their relation to several factors.

Abnormalities were found in 61 (44 per cent) cases and included T changes in 48 cases, S-T depression in 24 cases, conduction defects in 3 cases, prolonged Q-T in 6 cases, and a hypopotassemic pattern in 2 cases. An interesting feature was isolated negativity of the T wave in 5 cases and of the U wave in 1 case in the precordial leads.

The incidence of abnormalities was greater in the out-patient and in those with tachycardia, and greatest at the peak of the epidemic, suggesting some relation to the activity of the patient, the cardiac rate, and the epidemiology of the infection. These abnormalities were not related to the severity of the jaundice, the severity of the illness, or the serum protein levels.

The nature of the abnormalities suggested that myocardial ischemia, diffuse myocardial derangement, lesions of the bundle of His, and local electrolyte disturbance in the myocardium were some of the contributing factors.

Cardiac damage persisted in only 1 patient.

Summary in Interlingua

Esseva studiate 140 patientes con jalnessa resultante de hepatitis epidemic pro determinar le incidentia e le natura de anormalitates electrocardiographic e lor relation a varie factores.

Anormalitates esseva trovate in 61 casos (44 pro cento). Illos includeva alterationes de T in 48 casos, depression de S-T in 24, defectos de conduction in 3, prolongation de Q-T in 6, e un configuration hypokalemic in 2. Un aspecto interessante esseva isolate negativitate del unda T in 5 casos e del unda U in 1 caso in le derivationes precordial.

Le incidentia de anormalitates esseva plus alte inter patientes visitante e inter patientes con tachycardia e maximal al culmine del epidemic. Isto pareva indicar un influentia exercite per le activitate del patiente, le velocitate cardia, e le epidemiologia del infection. Iste anormalitates non esseva relacionate al severitate del jalnessa, al severitate del morbo, o al nivellos seral de proteina.

Le natura del anormalitates suggereva que le factores responsabile includeva ischemia myocardial, diffuse disrangiamiento myocardial, lesions del fasce de His, e local disturbances electrolytic in le myocardio.

Le insulto cardiac persisteva in solmente 1 patiente.

References

ELECTROCARDIOGRAPHIC ABNORMALITIES IN EPIDEMIC HEPATITIS


As to your method of work, I have a single bit of advice, which I give with the earnest conviction of its paramount influence in any success which may have attended my efforts in life—Take no thought for the morrow. Live neither in the past nor in the future, but let each day's work absorb your entire energies, and satisfy your widest ambition. That was a singular but very wise answer which Cromwell gave to Bellevire—"No one rises so high as he who knows not whither he is going," and there is much truth in it. The student who is worrying about his future, anxious over the examinations, doubting his fitness for the profession, is certain not to do so well as the man who cares for nothing but the matter in hand, and who knows not whither he is going.—William Osler, To His Students, 1849–1919.
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