Cardiac and Pulmonary Complications in Duchenne’s Progressive Muscular Dystrophy

By John Gilroy, M.D., Joseph L. Cahalan, M.D., Robert Berman, M.D., and Max Newman, M.D.

It is the purpose of this paper to present a clinical and pathologic study of myocardial involvement in seven previously unreported cases of the Duchenne form of progressive muscular dystrophy. The clinical signs of cardiac involvement in 139 cases and the electrocardiograms taken on the majority of these patients are also discussed. The frequent occurrence of pneumonia has proved to be a serious complication in nonambulatory patients and the treatment employed in such cases is presented. Finally, the problem of the terminal illness and the immediate cause of death are discussed.

The patients in this series have all been selected as cases of the Duchenne form of muscular dystrophy as defined by Walton and Nattrass. This corresponds to the “childhood group” of Tyler and Wintrobe. Walton and Nattrass define this group as (a) generally affecting male but rarely female subjects; (b) usually beginning in the first year of life but occasionally later; (c) transmitted as a sex-linked recessive character; and (d) usually progressing rapidly, giving total disability and often death in adolescence but sometimes with survival to adult life.

Material

This study involves 139 cases of progressive muscular dystrophy seen at the Muscular Dystrophy Clinic, Detroit Memorial Hospital, in the years 1958 and 1959. All patients were admitted to the hospital for diagnosis, and the majority has been re-examined at regular intervals in the clinic. The clinic serves the entire State of Michigan as a diagnostic and treatment center. Some patients from outlying areas were re-examined at other hospitals near their homes. The authors are indebted to a number of Michigan hospitals for allowing access to the records of these patients.

There were 131 male and eight female subjects. Ages varied from 4 to 35 years in the male patients and from 12 to 35 years in the female patients. There were nine Negro patients, all males. A positive family history was obtained in 52 cases or 37.5 per cent of our series. There were 14 sets of brothers, including one set of identical twins, two sets of two sisters and two sets of three brothers.

During the initial admission to the hospital all patients had a complete physical examination, chest x-ray, serum creatine and creatinine determinations, 24-hour urinary creatine and creatinine determinations, and electromyography. In addition, 111 patients had multiple-lead electrocardiograms. In the interpretation of the height of the R waves in the precordial leads the data tabulated by Lepeschkin, Nadas, and Sokolow and Friedlander in normal subjects were used.

The criteria for the diagnosis of progressive muscular dystrophy were as follows: history of progressive muscular weakness and disability beginning in the muscles of the pelvic girdle and the quadriceps femoris, absence of abnormal physical signs referable to the nervous system, weakness in affected muscles, muscular atrophy or pseudohypertrophy, creatinuria in the adult and excessive excretion of creatine in the child, abnormally high values for serum creatine, and dystrophic unit activity in the electromyogram.

In addition, there were two other factors which, when present, helped to confirm the diagnosis of progressive muscular dystrophy: a positive family history and a positive muscle biopsy. For purpose of analysis the patients have been divided into an ambulant group and a wheelchair group.

Fifteen patients died during the 2-year period under review. Eight patients died in Detroit Memorial Hospital, where six came to autopsy. Of the seven who died in other hospitals, one came to autopsy.

Clinical Manifestations of Cardiac Involvement

The commonest clinical abnormality in our patients was sinus tachycardia, which was noted in 124 cases. This was labile in almost all cases. The tachycardia was unpredictable in onset and duration and often appeared with minimal stimu-
Figure 1

Examples of electrocardiograms illustrating characteristics of various groups. In group A the R waves in V₁₋₃ are abnormally tall. In group B the R waves in V₁₋₃ are abnormally tall plus widening of the QRS interval to 0.10 second. In group C the QRS interval is widened to 0.10 second but R waves in V₁₋₃ are normal. In A+D tall R waves are present in V₂ and V₃, abnormal Q waves are present in I, aVL, V₅, and V₆ and T waves are inverted in aVL, V₂₋₅.

Clinical enlargement of the heart was found in only two patients. These two patients were also the only two with enlargement of the heart on chest x-ray. Both of these patients showed signs of congestive heart failure during their illness.

Murmurs occurred in 16 cases, were all systolic and of either grade-I or grade-II intensity. In three instances the murmurs were basal, nine were apical and two were at the left of the sternum. In two cases the murmurs were both apical and basal. All patients with a history of rheumatic
further examples of electrocardiograms illustrating characteristics of various groups. In B+D tall R waves are present in V1-3. QRS interval is widened to 0.10 second, and abnormal Q waves are present in 1, aVL, and V4-6. In C+D the R waves in V1-3 are normal, QRS interval is widened to 0.11 second, deep Q waves are present in 1 and aVL and T waves are flattened or slightly inverted in V4-6.

Electrocardiographic Changes

Electrocardiograms were taken in 111 patients (105 male and six female). A certain number of patients had two electrocardiograms during the 2-year period under study and others had tracings prior to 1958. The primary analysis refers to the latest record, but in every case where more than one tracing was available comparison with earlier tracings was made.

Hypertension was not noted in any of our patients.

Electrocardiographic Changes

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Thirty-six patients had electrocardiograms considered to be within normal limits. All six female patients had normal graphs. Abnormalities in the remaining 75 cases fall into four groups:

Group A. Abnormally tall R waves in unipolar chest leads over the right side of the heart (V1-3) —37 cases.

Group B. Incomplete right bundle-branch block or right ventricular hypertrophy combined with...
Duchenne's Progressive Muscular Dystrophy

Relation of electrocardiographic pattern to age of patient. Note that normal and group A electrocardiograms are predominant in younger age groups; groups B, C, and D, in older age groups.

Abnormally tall R waves in the right-sided chest leads V_{1-3} (i.e., a QRS interval between 0.10 and 0.12 second with or without an R-R' pattern). Since both types of tracings are thought to represent an intraventricular conduction defect, these cases have been grouped together. There were 15 cases in this group.

Group C. Incomplete right bundle-branch block or right ventricular hypertrophy alone—20 cases.

Group D. Evidence of diffuse myocardial damage. This was regarded as a late change. This group includes electrocardiograms showing S-T deviations, abnormal or inverted T waves, and abnormal Q waves. There were 19 cases in this group. Sixteen of these cases also showed changes compatible with groups A, B, or C. There were only three cases showing changes of diffuse myocardial damage alone.

Examples are shown in figures 1 and 2.

Relation of Electrocardiographic Pattern to Age of Patient

Figure 3 shows the electrocardiographic findings in relation to the age of patients. Normal tracings were seen predominantly in the younger age group. This is more striking if we delete the six normal graphs of female patients, four of which occurred in the age group over 20 and two in the 11 to 15 age group. Group D changes were not seen below 12 years of age.

Relation of Electrocardiographic Pattern to Duration of Disease

Normal electrocardiograms were found predominantly in patients who had progressive muscular dystrophy for less than 11 years. Normal tracings obtained in the 21-plus age group include three records from female patients. However, two male patients with long-standing disease and severe disability had normal electrocardiograms. Group A changes tended to predominate in patients with disease of less than 10 years' duration. Group D changes were not demonstrated in patients with...
Table 1

<table>
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<tr>
<th>Case no.</th>
<th>Cause of death</th>
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<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
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</tr>
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<td>7</td>
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<td>1</td>
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<td></td>
</tr>
<tr>
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</tbody>
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*Electrocardiograms not made.

progressive muscular dystrophy of less than 8 years' duration, and were seen in 11 patients of the 21-plus age group (fig. 4).

Relation of Electrocardiographic Pattern to Disability

Half of the patients in the walking group had normal electrocardiograms, but only 14 of the 65 patients in the wheelchair group had normal tracings. Group A changes were found to predominate slightly in the walking group. Group B and C changes were infrequent in the ambulant group and far more frequent in the wheelchair group. Group D changes, with one exception, all occurred in those patients unable to walk (fig. 5).

Electrocardiographic Patterns in Fatal Cases

Electrocardiograms were taken in 13 of the 15 fatal cases and they were all abnormal (table 1). Group D changes were noted, either alone or in combination with other group changes, in eight.

Comparisons with Previous Electrocardiograms

Previous electrocardiograms were available for comparison in 28 patients. Only five patients showed changes that were considered significant: one changed from normal to group C, one from group A to group A plus D, one from group C to group C plus D, and two changed from group A to group C.

Respiratory Complications of Progressive Muscular Dystrophy

During the 2 years under review 21 patients developed respiratory illnesses. Three of these patients had more than one attack of pneumonia in this period. Of the 15 patients who died the primary cause of death was pneumonia in five and the one patient who died from pulmonary embolus was found at autopsy also to have severe pneumonia.

The pneumonia usually began with an upper respiratory tract infection followed in a few days by an increased respiratory rate, paroxysmal ineffective cough, and a rise in temperature. At this stage examination usually revealed widespread rhonchi in all lung fields and crepitations at one or both bases. Chest x-ray usually revealed a pneumonic process confined to the basal segment of one or both lower lobes. The clinical and radiologic findings suggested that the pneumonitis was due to aspiration.

Treatment of Respiratory Complications

Patients with severe disability, especially those in the wheelchair group, have a reduced pulmonary reserve, and even a mild pulmonary illness reduces the pulmonary function to critical levels. The earliest possible initiation of vigorous therapy is imperative. Cultures were made of the sputum and combined with sensitivity studies to various antibiotics. Penicillin therapy was instituted immediately, and if the predominant organism later proved to be resistant to penicillin the appropriate antibiotic was then substituted. Oxygen was given by nasal catheter or in an oxygen tent. Suction was used frequently with a soft rubber catheter to clear secretions from the upper respiratory tract and a physiotherapist visited the patient frequently to encourage coughing and to help the patient raise bronchial secretions. The aid given by the physiotherapist depends upon the severity of the respiratory distress exhibited by the patient.
When there is only mild distress it is possible to position the patient in such a way as to drain the basal segments of the lower lobes. The patient is aided in deep breathing exercises and encouraged to cough while in this position. In severely ill patients changes in posture are not possible and the aid of the physiotherapist in encouraging coughing may be life-saving. Once improvement occurs change in posture may be attempted. Occasionally a patient shows evidence of accumulation of a large volume of secretion in the bronchial tree. Tracheotomy may then be necessary to facilitate suction of secretions and to eliminate much of the physiologic dead space. In some cases loss of a segment or more of lung due to atelectasis or pneumonia may have placed the patient in a state of anoxia, despite oxygen therapy. Such a patient may be carried through this critical period with intermittent positive pressure respiration.

**Cause of Death**

Fifteen patients died in the 2 years under review and it has been possible to obtain the clinical notes of the terminal illness in 13 of these cases.

Pneumonia was by far the commonest cause of death (table 1) and two patients were recorded as dying in “respiratory insufficiency.” Congestive heart failure was recorded as the cause of death in two cases and one patient died suddenly. One patient was admitted with a sudden episode of vomiting, diarrhea, and abdominal pain and died 36 hours after admission. One patient died from asphyxia following epistaxis and aspiration of blood and illustrates that aspiration is an ever-present hazard in these cases with poor expiratory reserve and dystrophic respiratory muscles.

**Autopsy Material**

Autopsy findings in the seven cases are similar and are summarized in table 2. All patients were under 25 years of age, were severely disabled, and had been confined to wheelchairs for 5 years or more. All showed evidence of dystrophic involvement of the myocardium, and in four cases the condition was recognizable macroscopically. Cardiac hypertrophy was mentioned in two cases, both of which showed some dilatation of one or both ventricles, while a third case showed a minor degree of left ventricle dilatation.

Histologic examination of the heart (figs. 6 and 7) showed an almost identical pattern in all seven cases. Sections of myocardium varied from areas of well-preserved fibers with slightly or moderately enlarged nuclei to areas of extensive replacement by connective tissue. Near the areas of fibrosis many muscle fibers were hypertrophied with prominent nuclei, whereas others were atrophic with pyknotic nuclei, but the cytoplasm was acidophilic, similar to normal muscle, and striations were preserved. The difference between myocardial fibers and connective tissue was often indistinct, with gradual blending of one into the other. Individual fibers appeared to have an open end where sarcolemma became shadow-like or finely fibrillar, blending with adjacent connective tissue. Occasionally the muscle sheath appeared to persist and became coextensive with the components of sclerotic area. Foci of fibrosis were frequently perivascular but
Autopsy Findings

<table>
<thead>
<tr>
<th>Age</th>
<th>Cause of death</th>
<th>Duration of disease (yr.)</th>
<th>Unable to walk (yr.)</th>
<th>Cardiac hypertrophy</th>
<th>Cardiac dilatation</th>
<th>Dystrophic involvement</th>
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<td>Yes</td>
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<td>8</td>
<td>Yes</td>
<td>Right ventricle</td>
<td>Yes</td>
</tr>
<tr>
<td>24</td>
<td>Epistaxis, aspiration of blood</td>
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<td>13</td>
<td>No</td>
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<tr>
<td>16</td>
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<td>6</td>
<td>No</td>
<td>Left ventricle</td>
<td>Yes</td>
</tr>
<tr>
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<td>Diarrhea, sudden death</td>
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<tr>
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<td>11</td>
<td>7</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

In all cases the myocardium was firm. Gastrointestinal involvement was not seen.

Table 2

Discussion

There seems little doubt that myocardial involvement in advanced cases of progressive muscular dystrophy is common. It is not known at what stage during the disease myocardial involvement first occurs but electrocardiographic changes are often present in the young, indicating early involvement. The seven autopsied cases here presented were advanced, seriously disabled patients in common with those reported by other authors. It is possible that myocardial involvement can be demonstrated earlier in a majority of cases. In four of our cases dystrophic changes were obvious macroscopically and were recognized immediately. In three cases, however, typical changes were seen only microscopically. In material of this type only careful search will demonstrate the dystrophic changes. In 1922 Globus observed "Probably myocardial changes would be more frequently found in progressive muscular dystrophy if the heart is systematically studied in every case."

Tachycardia was the commonest clinical manifestation of heart involvement. This occurred early, but was so labile and unpredictable that its significance is obscure. Other signs of cardiac involvement (cardiomegaly and congestive heart failure) were uncommon and, when present, were found only in most advanced cases. It is our belief that the severe restrictions imposed on the patient's physical activity by the skeletal muscle involvement protect the patient from overt signs of heart failure.

Electrocardiographic changes, although not invariable, were common in our series and demonstrated a pattern of abnormalities that could be considered almost specific. Tall R waves in right precordial leads (group A) have been described before and have been amply demonstrated here. There is a tendency for this change to be observed in patients of the younger age group who have had muscular dystrophy for only a few years, but it sometimes was present as the sole electrocardiographic abnormality in older patients.

Incomplete right bundle-branch block, with and without abnormally tall R waves in right precordial leads (groups B and C), tended to occur in patients who had had muscular dystrophy for a number of years and was cer-
tainly more frequent in the more severely disabled wheelchair group. In view of the fact that there are two examples in our series of transition from a finding of tall R waves in right precordial leads (group A) to incomplete bundle-branch block (group C), it is interesting to postulate that there may be a transition from group A to group C, possibly via group B as the disease progresses. This has already been suggested by Gailani et al., who had a similar record on one of their patients. These authors further eliminated the possibility of pulmonary hypertension in their patients by cardiac catheterization, suggesting that this pattern might well represent a true conduction defect due to dystrophic myocardial damage. The electrocardiographic patterns observed in this series support this view. There was no evidence to suggest that the tall R waves were due to an unusual position of the heart as suggested by Weisenfeld and Messinger. There is, however, a possibility that the electrocardiographic changes encountered in groups A, B, and C are due to right ventricular hypertrophy in certain cases. Although right ventricular hypertrophy is not common in autopsy material, the one case in this series with definite evidence of ventricular hypertrophy showed abnormally tall R waves in right precordial leads.

There is good evidence for the interpretation of the changes of diffuse myocardial damage (group D) as late changes. All cases with this type of record had the disease for 8 years or more. All save one were severely disabled patients in the wheelchair group. Abnormally deep Q waves in some of these cases gave a striking resemblance to the pattern of myocardial infarction, which one would not expect to find in this young age group, nor was this demonstrated at autopsy. The suggestion of Ruben and Buchberg that the dystrophic muscle may act in a fashion similar to infarcted muscle with the production of deep Q waves is supported by our findings.

Pneumonia is unquestionably the commonest cause of death in progressive muscular dystrophy. We believe that heart disease may be an important secondary cause of death in cases where pneumonia is the primary cause. The diseased myocardium must be unduly sensitive to anoxia. This may explain the sudden death in some patients with pneumonia. Muscular dystrophy patients sometimes die suddenly with no preliminary warning. It may be that patients in this group have dystrophic involvement of the myocardium and are on the verge of congestive heart failure, so that heart failure may be precipitated abruptly by a sudden demand on limited reserve.

There are a number of reports in the literature of death in progressive muscular dystrophy following a brief episode of abdominal pain, vomiting, and diarrhea. One patient in our series presented with these symptoms and four patients had intermittent attacks of abdominal pain in the few weeks prior to death. There was no evidence of dystrophic involvement of the smooth muscle of the gastrointestinal tract as described by some authors. It is possible that abdominal pain recorded in the late stages of this disease is often due to fecal impaction, a common complication in bedridden patients. Even here myocardial disease may be an important contributory cause of death, since the dystrophic myocardium would tolerate poorly the dehydration and electrolyte imbalance that accompany vomiting and diarrhea.

Arrhythmias were not observed in our series. Apparently they are not a part of the clinical picture described here.

**Summary and Conclusions**

Cardiac involvement in progressive muscular dystrophy of the Duchenne type is a common complication of this disease. The essential pathologic changes consist of atrophy of cardiac muscle and replacement of the fibers by a collagenous connective tissue that blends with the sarcoplasm of the adjacent cardiac muscle fibers. There is no fibroblastic proliferation in the involved areas, and the cellular content of the connective tissue probably represents surviving cardiac nuclei. Fat replacement as seen in skeletal muscle in progressive dystrophy.
muscular dystrophy is not a feature of the dystrophic process in the myocardium.

The commonest clinical manifestation of myocardial involvement is a labile sinus tachycardia. Congestive heart failure is a rare occurrence.

Electrocardiographic abnormalities are encountered frequently. The early appearance of abnormally tall R waves in right precordial leads may progress to the development of incomplete right bundle-branch block with eventual disappearance of the tall R waves. At a later stage evidence of diffuse myocardial damage may appear, manifested by inverted T waves, ST-segment deviation, and abnormal Q waves.

Pneumonia is a frequent complication in advanced cases of progressive muscular dystrophy and is the commonest cause of death. When this complication appears, vigorous therapy is imperative and should include antibiotics, physical therapy to clear the airways, and positive-pressure respiration.

Occurrence of sudden death in patients with dystrophic involvement of the myocardium may be due to the abrupt onset of congestive heart failure following a sudden demand on a limited cardiac reserve. This may be an important contributory cause of death where the primary cause is pneumonia, and may also be a factor in the sudden death that sometimes follows attacks of abdominal pain, vomiting, and diarrhea.

References


Conjectures and Some Conclusions

From what is known and explored thus far, I think it is sufficiently established that there is electricity in animals, which, with Bartholinus and others, we may be permitted to call by the general name of animal electricity. This, if not in all, yet is contained in most parts of animals; but manifests itself most conspicuously in muscles and nerves.

The peculiar and not previously recognized nature of this seems to be that it flows from muscles to nerves, or rather from the latter to the former, and that it traverses there either an arc or a series of men or any other conducting bodies which lead from nerves to muscles by a shorter and quicker way, and flows most speedily through them from the former to the latter.

From this, moreover, two consequences seem chiefly to ensue, namely, that the electricity in these parts is, one positive, as we may believe, the other negative, and that one is wholly distinct in nature from the other; for when equilibrium is established, there is no motion, no excursin of electricity, no phenomenon of muscular contraction.

But forsooth, it is difficult to define in which of the designated parts one electricity resides, in which the other; whether, for example, one in muscle, the other in nerve, or both in one and the same muscle, and from which part it flows. In this obscurity of things, however, if it is permissible to have an opinion, my mind inclines towards placing the location of both kinds of electricity in muscle.—Luigi Galvani. Commentary on the Effect of Electricity on Muscular Motion. Translated by Robert Montraville Green, M.D. Cambridge, Massachusetts, Elizabeth Licht, Publisher, 1953, p. 60.
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Circulation. 1963;27:484-493
doi: 10.1161/01.CIR.27.4.484

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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