Stroke in Duchenne Muscular Dystrophy
A Retrospective Longitudinal Study in 54 Patients

Martin Winterholler, MD; Christian Holländer, MD; Frank Kerling, MD; Irina Weber, MD; Sven Dittrich, MD; Matthias Türk, MD; Rolf Schröder, MD

Background and Purpose—Duchenne muscular dystrophy (DMD) is the most frequent skeletal muscle myopathy. Nearly all patients develop cardiomyopathy in their second decade of life. The purpose of this study was to evaluate the frequency, cause, and outcome of stroke in a German cohort of patients with DMD.

Methods—Retrospective analysis of medical records of 54 DMD patients, who lived in a regional facility for handicapped people (Wichernhaus Altdorf, Germany) between 1963 and 2013.

Results—Fifty-four DMD patients were followed up for 7.4 years on average. Mean age at admission and discharge from the long-term care facility or death were 11.4 and 18.8 years, respectively. Covering a total observation period of 400 patient-years, we identified 4 DMD patients with juvenile arterial ischemic strokes. Off-label systemic thrombolyis in 2 patients resulted in a nearly complete regression of stroke-related symptoms, but 1 patient died of septic pneumonia and cardiac failure 24 days after thrombolysis therapy. In the other 2 patients, who had their ischemic strokes in 1994 and 1998, severe infarction-related symptoms persisted, and 1 patient died 13 days later. DMD-associated cardiomyopathy without evidence of atrial fibrillation was the only risk factor for ischemic stroke in all patients.

Conclusions—This study indicates an increased risk for ischemic strokes in DMD patients. Regular cardiological assessment of all DMD patients is mandatory to evaluate the individual risk profile for cardioembolic events and to adapt therapeutic strategies. (Stroke. 2016;47:2123-2126. DOI: 10.1161/STROKEAHA.116.013678.)

Key Words: cardiomypathy ■ Duchenne muscular dystrophy ■ dystrophin ■ stroke ■ thrombolytic therapy

Duchenne muscular dystrophy (DMD) is the most frequent muscular dystrophy with an incidence of 1 in 3600 to 6000 male births. The disease usually manifests between the third and fifth year of life and leads to a steady decline in strength and motor function, contractures, and loss of ambulation between 9 and 13 years of age. Furthermore, the lack of dystrophin protein expression in cardiac tissue of DMD patients is frequently associated with cardiomyopathy. The diagnosis of DMD is nowadays established by mutation analysis of the dystrophin gene or lack of dystrophin protein expression in diagnostic muscle biopsies. In years previous to the identification of the underlying dystrophin gene defect, DMD was diagnosed on the basis of its typical clinical presentation, very high creatine kinase levels, and dystrophic muscle biopsy findings. To date, no curative therapy is available for DMD, and most patients die in the second to forth decade of life because of respiratory or cardiac failure. Although cardiomyopathy is a frequent and prognosis-defining feature of DMD, just a small number of cases with stroke in DMD patients has been reported to date (Table). In this study, we retrospectively analyzed the frequency, cause, and outcome of stroke in a German cohort of 54 DMD patients, who lived in a regional facility for handicapped people between 1963 and 2013.

Methods

To analyze the frequency, cause, and outcome of ischemic and hemorrhagic stroke in DMD, we retrospectively reviewed the clinical data of 59 male patients, who lived at the Wichernhaus in Altdorf, a specialized learning and living facility for handicapped children and young adults near Nuremberg in Germany, between 1963 and 2013. Data were collected from the DMD patients’ medical files obtained from the treating Department of Neurology and Department of Orthopedics of the Rummelsberg Hospital, a teaching hospital of the Friedrich-Alexander University of Erlangen-Nürnberg, Germany, and from a local general practitioner serving the facility. Data collection was authorized by the ethics committee of the Friedrich-Alexander University of Erlangen-Nürnberg. Informed consent from patients was not required based on the retrospective analyses of medical records.
Diagnosis of DMD was made according to the criteria at the respective time. Diagnostic criteria for likely DMD were (1) disease manifestation between the third and fifth year of life with proximal muscle weakness and calf hypertrophy; (2) loss of ambulation between 9 and 13 years; (3) death before the age of 25 or 35 years without/with ventilation support, respectively; (4) high creatine kinase levels (>15× upper limit of normal); and (5) dystrophic pattern in muscle biopsy if performed. Diagnostic criteria for definite DMD were additional (1) report of a DMD causing dystrophin gene mutation or (2) report of negative dystrophin immunostaining in a muscle biopsy.

Medical records were analyzed with regard to the diagnosis of ischemic or hemorrhagic stroke. Stroke was defined as acute onset of a focal neurological deficit with proof of infarction or hemorrhage in a corresponding brain territory by computed tomographic imaging or magnetic resonance imaging (MRI).

The 95% confidence interval for incidence rate was calculated based on the Byar method.8

Results

Our retrospective analysis of the medical records of 59 male individuals identified 54 patients fulfilling the diagnostic criteria for definite (n=11) or likely (n=43) DMD. In the remaining 5 individuals, at least 1 DMD-defining criterion was not fulfilled, resulting in exclusion from further analysis.

The analysis of the 54 DMD patients covered a total observation time of 400 patient-years with a mean follow-up period of 7.4 (range, 0.2–17.3) years. Mean age at admission and discharge from the long-term care facility or death were 11.4 (range, 3.8–22.1) and 18.8 (range, 12.1–35.0) years, respectively. In this cohort, we identified 4 individuals with arterial ischemic strokes, yielding an incidence rate of 1 in 100 patient-years (95% confidence interval, 0.3339–2.3751; respectively). In this cohort, we identified 4 individuals with arterial ischemic strokes, yielding an incidence rate of 1 in 100 patient-years (95% confidence interval, 0.3339–2.3751; respectively).

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Table. Overview of Newly and Previously Reported DMD Patients With Ischemic Stroke

<table>
<thead>
<tr>
<th>Publication</th>
<th>Age</th>
<th>Vascular Territory</th>
<th>Thrombolysis</th>
<th>Cardiac Involvement</th>
<th>Outcome/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winterholler et al</td>
<td>16 y (2013) pt 1</td>
<td>MCA (right)</td>
<td>Yes</td>
<td>DCM</td>
<td>Marked recovery/ cardiac failure/died</td>
</tr>
<tr>
<td></td>
<td>16 y (2012)/pt 2</td>
<td>MCA (left)</td>
<td>Yes</td>
<td>Red LVEF</td>
<td>Marked recovery</td>
</tr>
<tr>
<td></td>
<td>13 y (1996)/pt 3</td>
<td>Left hemisphere</td>
<td>No</td>
<td>DCM</td>
<td>Aphasia, hemiparesis/died</td>
</tr>
<tr>
<td></td>
<td>16 y (1994)/pt 4</td>
<td>MCA (right)</td>
<td>No</td>
<td>Red LVEF</td>
<td>Aphasia, hemiparesis</td>
</tr>
<tr>
<td>Tsakadze et al</td>
<td>17 y</td>
<td>BA/(PCA left)</td>
<td>NA</td>
<td>DCM</td>
<td>Afterward OAC</td>
</tr>
<tr>
<td>Gimenez-Muñoz et al</td>
<td>21 y</td>
<td>MCA (right)</td>
<td>NA</td>
<td>DCM/cardiac thrombus</td>
<td>Afterward OAC</td>
</tr>
<tr>
<td>Ikeniwa et al</td>
<td>21 y</td>
<td>MCA (left)</td>
<td>NA</td>
<td>DCM</td>
<td>NA</td>
</tr>
<tr>
<td>Díaz Buschmann et al</td>
<td>13 y</td>
<td>MCA (2×; left and right)</td>
<td>NA</td>
<td>DCM</td>
<td>Hemiparesis</td>
</tr>
<tr>
<td>Hanajima et al</td>
<td>5 pt/16–20 y</td>
<td>5× MCA (left and right)</td>
<td>NA</td>
<td>DCM (all)+AF (1×)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>1 pt</td>
<td>1× MCA (right)</td>
<td>NA</td>
<td>None</td>
<td>Autopsy finding</td>
</tr>
<tr>
<td>Matsuishi et al</td>
<td>4 y</td>
<td>BA stenosis; 3 events</td>
<td>NA</td>
<td>LHV</td>
<td>NS</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; BA, basilar artery; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; LHV, left ventricular hypertrophy; MCA, middle cerebral artery; NA, no data available; NS, not specified; OAC, oral anticoagulation; PCA, posterior cerebral artery; pt, patient; red, reduced; and TIA, transient ischemic attack.
been diagnosed with severe dilated cardiomyopathy with enlarged left atrium and ventricle but no relevant valve disease. He died 13 days after his ischemic stroke. Unfortunately, no further information on the stroke workup and cause of death are available. Patient 4 is a tetraparetic 16-year-old DMD patient, who developed acute severe aphasia and worsening of his preexisting left arm pareses. Cerebral MRI demonstrated an infarction in the territory of the right middle cerebral artery. Transthoracic and transesophageal echocardiography revealed reduced left ventricular systolic function without evidence of atrial or ventricular enlargement, thrombus formation, septal defect, or relevant valve disease. He had an unfavorable clinical outcome with persistence of his central nervous system–related symptoms.

Additionally, all documented 12-lead ECGs (all patients) and Holter ECGs (just patients 1 and 2) showed sinus rhythm. Stroke workup of patient 1, 2, and 4 did not reveal any further general vascular risk factors. Laboratory screening for coagulation disorders and vasculitis in patient 1 and 2 were unremarkable.

Discussion

Ischemic strokes in DMD have previously been described in a small number of patients, but epidemiological data on cerebral infarction in DMD and in primary myopathies in general are scarce. In a prospective observational study published in Stroke 1987, none of 52 DMD patients were reported as having cerebral infarction. A Japanese questionnaire-based study published in 1996 reported 5 cerebral infarctions among 665 DMD patients within the year 1993, yielding a stroke incidence rate of 0.75 per 100.6 Covering 54 DMD patients and a total observation period of 400 patient-years, our study identified 4 patients with arterial ischemic strokes manifesting between 13 to 16 years of age, yielding an incidence rate of 1 per 100 patient-years. This is much higher than the overall arterial ischemic stroke incidence in childhood, which is quoted as 1.6 per 100,000.11

Off-label thrombolysis with recombinant tissue-type plasminogen activator in 2 boys led to a swift and marked remission of their stroke-related deficits. In line with previously reported data about safety of alteplase in childhood ischemic stroke, systemic thrombolysis in both juveniles was without adverse events. MRI along with stroke workup point to further information on the stroke workup and cause of death. In our DMD boys seems likely because of cardioembolic events on the basis of their preexisting cardiomyopathy.

Although almost all DMD patients, who benefit from major improvements in symptomatic multidisciplinary care, will have cardiomyopathy in adulthood, there are currently no standard guideline recommendations for preventive anticoagulation or antiplatelet therapy in juvenile and adult DMD patients. Thus, regular cardiovascular assessment of all DMD patients is mandatory to evaluate the individual risk profile for cardioembolic events and to adapt therapeutic strategies.15

Acknowledgments

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Disclosures

S. Dittrich is a principal investigator of the multicenter study “Effect and Safety of Preventive Treatment With ACE Inhibitor and Beta Blocker on the Onset of Left Ventricular Dysfunction in Duchenne Muscular Dystrophy,” which is funded by the German Ministry of Health (support code 01KG0912, Eudra CT number 2009-009871-36). The other authors report no conflicts.

References


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SUPPLEMENTAL MATERIAL

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Supplemental Figure I. Representative MR-imaging of the brain of patient 1 and 2 acquired one day after onset of stroke. A/B Fluid-attenuated inversion recovery (FLAIR) – sequence (A) of patient 1 demonstrates demarcation of a territorial infarction in the right MCA-territory without evidence for vascular pathology in time-of-flight MR-angiography (TOF-MRA) (B). Considering all clinical findings this constellation suggests primarily a transient occlusion of the proximal MCA. C/D FLAIR-sequence (C) of patient 2 demonstrates demarcation of a territorial infarction of the left basal ganglia. Note the partial occlusion of the M1-segment of the left MCA (arrow) in TOF-MRA (D).