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BACKGROUND: Duchenne muscular dystrophy (DMD) leads to progressive impairment of muscle function, respiratory failure and premature death. Longitudinal data on the course of physical disability and respiratory function are sparse. OBJECTIVES: To prospectively assess physical impairment and disability, respiratory function and survival in DMD patients over several years in order to describe the course of the disease with current care. METHODS: In 43 patients with DMD, aged 5-35 years, yearly assessments of physical disability by the Duchenne muscular dystrophy physical Impairment and Dependence on care (DID) score ranging from 9 (no disability) to 80 (complete dependence), and forced vital capacity (FVC) were obtained over a mean +/-SD time interval of 5.4 +/-2.1 years. RESULTS: DID scores were correlated with age according to a hyperbolic function (f=85.3*age/(10.05+age), R=0.62, P<0.0001). FVC declined exponentially with age (f=139.1*exp(-0.08*age)), R=0.52, P<0.0001. Mean +/-SD age at which patients lost their ambulation was 9.4 +/-2.4 years and they became dependent on an electro-wheelchair at 14.6 +/-4.0 years. The age at beginning of assisted ventilation was 19.8 +/-3.9 years, Three patients deceased during the observation period. The estimated probability of survival to age 30 years was 85%, median survival was 35 years. CONCLUSIONS: Our detailed observations of the progression of physical disability, dependence on care and respiratory impairment in DMD patients from childhood to adult life is valuable for predicting the clinical course with current medical care. Compared to historical data, survival has considerably improved.

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Disability and Survival in Duchenne Muscular Dystrophy

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Abstract

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Objectives: To prospectively assess physical impairment and disability, respiratory function and survival in DMD patients over several years in order to describe the course of the disease with current care.

Methods: In 43 patients with DMD, aged 5-35 years, yearly assessments of physical disability by the Duchenne muscular dystrophy physical Impairment and Dependence on care (DID) score ranging from 9 (no disability) to 80 (complete dependence), and forced vital capacity (FVC) were obtained over a mean ±SD time interval of 5.4 ±2.1 years.

Results: DID scores were correlated with age according to a hyperbolic function ($f=85.3*age/(10.05+age)$, $R=0.62$, $P<0.0001$). FVC declined exponentially with age ($f=139.1*\exp(-0.08*age)$), $R=0.52$, $P<0.0001$. Mean ±SD age at which patients lost their ambulation was 9.4 ±2.4 years and they became dependent on an electro-wheelchair at 14.6 ±4.0 years. The age at beginning of assisted ventilation was 19.8 ±3.9 years, Three patients deceased during the observation period. The estimated probability of survival to age 30 years was 85%, median survival was 35 years.

Conclusions: Our detailed observations of the progression of physical disability, dependence on care and respiratory impairment in DMD patients from childhood to adult life is valuable for predicting the clinical course with current medical care. Compared to historical data, survival has considerably improved.

Introduction

Duchenne Muscular Dystrophy (DMD) is the most common form of the inherited muscular dystrophies affecting approximately one in 3300 male births. The disorder is caused by mutations in the gene located at Xp21 which codes for the dystrophin protein. DMD leads to progressive muscular weakness, severe physical disability and ultimately death. [1,2] Most DMD patients become wheelchair-bound in childhood, and they depend largely on their parents for their daily activities and care. [3] In more advanced stages of the disease, the progressive spinal and chest wall deformity and the impairment of respiratory muscle function leads to hypercapnic respiratory failure, and cardiac muscle involvement may entail congestive heart failure. [4] Recent studies suggest that non-invasive positive-pressure ventilation and other supportive measures prolong survival of patients with DMD well into adulthood. [5,6]

With prolongation of life, physical impairment and dependence on care increases due to the progressive nature of the disorder but data on this topic from adult DMD patients is limited or outdated. [1,3,7,8] We are aware of only one cohort for whom longitudinal data on physical disability in adult patients with DMD was reported. [7,9] Prediction of profiles was limited by the small number of patients included, and a relatively short follow-up time. [7] Knowledge of the course of physical impairment in DMD is of great importance to patients, parents and health care providers because it allows having a realistic outlook on the progression of the disease, facilitates planning of long-term care, and defines specific problems and needs of DMD patients.

Previously, conventional evaluation of physical impairment has been mainly focused on motor deficits based on measurement of muscle strength [3,10] but such measures might not appropriately capture the clinically relevant functional disabilities of the patients. To overcome this limitation, several scores have been proposed to assess physical impairment in patients with neuromuscular diseases but they were not specifically designed for DMD patients of various age ranges. [11-15] Therefore, we recently introduced a simple to use, DMD-specific score that assesses the various aspects of physical impairment and dependency on help by others and technical aids [5] that we termed DID-score (standing for Duchenne muscular dystrophy physical Impairment and Dependency score).

In this study, we applied the DID score to prospectively investigate the long-term course of physical impairment and dependence on care, along with lung function and survival in a cohort of 43 patients with DMD. The aim was to provide current profiles of the clinical presentation and the natural history of DMD from childhood into adult life in order to predict the individual clinical course of the disease with current medical care.

Methods

Patients

Patients with DMD living or attending school in a facility specialized in the care of patients with muscular dystrophy, the Mathilde-Escher-Heim, Zurich, were prospectively enrolled during the period from 1999 to 2006. The diagnosis of DMD was based on standard criteria comprised of progressive symmetrical muscle weakness and other signs and symptoms starting before the age of 5 years, elevated serum creatinine kinase activity, muscle biopsy and/or genetic analysis, and, in some, a family history consistent with X-chromosome-linked recessive inheritance. [16] Information on genetic analysis was available from 10 patients (9 patients had a deletion in at least one of the exons 48-52 of the DMD gene locus, whereas a duplication mutation was found in 1 patient). The study protocol was approved by the local ethical committee and patients gave informed consent to participate.

Measurements

A physical examination, including measurement of body weight and height, was performed and body mass index was calculated. Height was used for calculation of reference values of pulmonary function. It was determined by a flexible ruler fitted along the contours of the body,

from the head, along the vertebral spine and the backside of the legs, to the heels to account for kyphoscoliosis and leg contractures.

Spirometry was performed in the sitting position with a flow meter attached to a flanged rubber mouthpiece with the nose occluded. [17] Reference values for ages up to 17 years [18] and above [19] were computed.

Physical impairment and the inability to perform activities of daily living and dependence on others and on technical aids was evaluated with the DID score specifically developed at our center for DMD patients as described previously (appendix). [5] The DID score consists of the following eight aspects of daily life: mobility without technical aids, mobility with technical aids, transfers (e.g. from bed to wheelchair), changes of body position, dressing, static body control, feeding, and breathing. Each aspect is rated with up to 10 points, with higher scores reflecting greater impairment and disability. The sum score of all eight domains is calculated as a measure of overall impairment, disability and dependency with a minimal value of 9 (no impairment in any of the domains) and a maximum value of 80 points (completely impaired and dependent on help by others in all domains). The DID score was prospectively applied on a yearly basis.

For evaluation of inter-observer agreement, 2 experienced physical therapists independently applied the DID score to all the DMD patients alive in 2006.

Data analysis

Data are expressed as means ± SD. Regression analysis was used to determine the relationships among the DID score, forced vital capacity and age. Survival probability was calculated by the Kaplan-Meier method. The inter-observer-agreement between DID scores obtained by two observers was evaluated by Pearson's correlation and by calculating the mean difference (bias) and limits of agreement (±2 SD). [20] A probability <0.05 was considered statistically significant.

Results

Demographics

Forty-three DMD patients with a mean ±SD age of 15.3 ±5.2 years, and a BMI of 20.0 ±7.3 kg/m^2 at enrolment were followed over a time period of 5.4 ±2.1 (range 1 to 8) years. The course of weight, height and BMI is shown for selected ages in the table.

Physical Impairment and Dependency

In total, 227 yearly assessments were performed in the 43 patients. Milestones of the clinical course in DMD patients are described in the table. Individual trends of DID scores over time are shown in figure 1. The progression of physical impairment and disability as reflected by the DID score at any particular age was strongly correlated with age (in years) according to the hyperbolic function: DID score = 85.33*age/(10.05+age), $R=0.62$, $P < 0.0001$. The DID scores of 19 out of 20 patients (95%) whose initial score was above the fitted hyperbolic line, remained above this line. Thus, an advanced disability at the first observation was associated with a subsequent further continuous progression in disability. The DID score of only 9 patients crossed the fitted line on a total of 11 occasions, 8 in upward direction (worse), but only 3 in downward direction (improved) (χ^2-test, $p=0.03$).

Follow-up assessments of the 8 domains of the DID score revealed that the impairment in the domains 'mobility without technical aid', 'mobility with technical aid', 'transfer', 'changes of body position' and 'getting dressed' started around the age of 5 years and increased rapidly until the age of 10 to 15 years with a subsequent plateau at the maximum level of disability. In contrast, the progression of impairment in the domains 'static body control', 'eating and drinking' and 'breathing' was moderate in early life but accelerated in adulthood (figure 2).

For some domains of the DID score specific milestones in the clinical course of the disease are listed in the table. The mean age at which patients lost their ambulation was 9.4 ±2.4 (range 6 to

15) years. They became dependent on an electro-wheelchair at 14.6 ±4.0 (range 11 to 28) years. Thirty-three patients (77%) had undergone spinal fusion surgery at a mean age of 14.2 ±2.6 (range 8 to 21) years. The age when food and drinks had to be given to a patient by a caregiver was 18.2 ±4.2 (range 12 to 23) years, and the age at which 22 of the patients required assisted mechanical ventilation was 19.8 ±3.9 (range 14 to 31) years. In 8 patients (19%) a gastrostomy had been performed at a mean age of 24.7 ±4.9 (range 20 to 34) years due to feeding problems.

Table. Milestones in the clinical course of Duchenne muscular dystrophy

	Age 10 y (n=8)	Age 15 y (n=16)	Age 20 y (n=12)	Age 25 y (n=7)	Age 30 y (n=3)
Mobility w/o technical aids	8: crawling on elbows	10: moving impossible without technical aids			
Mobility with technical aids	3: wheelchair driving without motor	5: electro-wheelchair driving without neck-stabilisator, every terrain	6: electro-wheelchair driving with orthopaedic aids		
Transfer	6: transfer chair to wheelchair without help, with sliding aid	8: transfer chair to wheelchair with help, with sliding aid			10: transfer chair to wheelchair only by lifting the patient
Changes of body position	6: change from supine to side-position without help	8: change position of head and arms without help	9: change position of head without help		
Getting dressed	5: getting dressed in seated position	7: getting dressed in seated position, needs full help	8: getting dressed in supine position		
Static body control	6: sitting on the floor without help	7: sitting on a chair without a lean	8: sitting on a chair with a lean, head control without help		
Eating and drinking	2: eating at table with fork/knife without help		3: eating at table with fork/knife with help	5: meal must be given to patient	
Breathing	2: normal breathing, but reduced FVC		4: PPV during night	6: PPV during night, sometimes during day	
FVC (% pred)	83 ±15	42 ±23	25 ±18	16 ±16	18 ±14
Height (cm)	142 ±10	154 ±8	165 ±10	167 ±12	171 ±5
Weight (kg)	46 ±21	52 ±21	63 ±22	64 ±25	56 ±12
BMI (kg/m^2)	22.2 ±8.1	21.7 ±8.0	23.3 ±8.0	22.6 ±6.2	19.3 ±4.2
Survival probability (%)	100	100	100	85	85

Values followed by ":" are means of the DID score at the corresponding age; values of forced vital capacity (FVC, % predicted), height, weight and body mass index (BMI) are means ±SD; PPV = assisted positive pressure ventilation. FVC values available from 4 patients at age 10y, 7 at age 15, 12 at age 20, 6 at age 25, and 2 at age 30.

DID scores obtained independently by 2 observers in 40 patients were closely correlated (r=0.96, P<0.0001) with a mean difference of 2.1 points and limits of agreement (± 2 SD of bias) of ±4.6 points.

Lung function

Forced vital capacity (FVC) revealed an exponential decline with age according to the function: FVC =139.1*exp(-0.08*age), R=0.52, P < 0.0001 (Figure 3). Mean age at which FVC fell below 1 L was 18.1 ±5.0 (range 13 to 31) years.

Twenty-two of the 43 patients (51%) received long-term assisted mechanical ventilation for chronic respiratory failure. Seventeen of these patients were ventilated non-invasively with a nasal or oral-nasal mask, and 5 patients via tracheotomy. Mean age at the beginning of mechanical ventilation was 19.8 ±3.9 (range 14 to 31) years, mean FVC was 0.73 ±0.34 L (20 ±10 % of predicted).

Survival

Only 3 of the 43 DMD patients died during the follow-up time. One patient died because of heart failure due to cardiomyopathy at the age of 35 years, one patient died suddenly 8 days after tracheotomy at the age of 22 years, and one patient died due to respiratory failure at the age of 24 years. Kaplan-Meier analysis revealed a median survival of 35 years. The probability of surviving 10 years after initiation of assisted mechanical ventilation was 68% (figure 4).

Discussion

We prospectively investigated the clinical course in patients with Duchenne muscular dystrophy from childhood to adult life and identified milestones of disease progression. The strength of our study is the detailed observation of the course of physical impairment and dependence on care over several years by using the DID score along with spirometry and survival in a large patient cohort. The current update on the clinical course of DMD is valuable for patients, families and health professionals as an adjunct in planning medical care and future life. The median survival of 35 years compares favourably to historical data and presumably reflects advances in assisted mechanical ventilation and other supportive care.

We recorded the clinical course of DMD patients using a recently introduced instrument, the DID score, that assesses eight different aspects of impairment and disability in daily life. [5] The DID score quantifies the physical impairment in DMD patients with high inter-observer agreement and identified clinical milestones such as the loss of ambulation at a mean age of 9.4 years, dependence on an electrical wheel chair at 14.6 years, the dependence on being dressed and fed by caregivers at 18.2 years and the requirement for assisted mechanical ventilation at 19.8 years. In contrast to other (generic) scores such as the index of ADL which was designed for the elderly [11], the DID score incorporates aspects of disability typical for DMD patients and relevant to their entire life span. Similar to the EK-score which is focused on disability in non-ambulatory DMD patients [15] the DID score assesses wheelchair mobility, transfer, static body control and dependence on help with eating and drinking. But unlike the EK score, the DID score also incorporates observations on mobility without technical aids (appendix, domain 1), and specifically addresses the need for assisted mechanical ventilation (appendix, domain 8) which has become an essential, life saving component of care.

The DID scores progressed rapidly in childhood and subsequently approached maximal values corresponding to nearly total dependence on caregivers and technical aids such as a wheel-chair and mechanical ventilation. Individual grades of disability at a certain age varied, possibly

related to differences in treatment and life style [21-23], although all DMD patients in our study received medical care by the same institution. We observed an increase in DID scores over time according to a hyperbolic function (figure 2). Almost all patients (95%) who initially scored above the regression line did so in every subsequent follow-up (figure 1). Scores for the 8 domains incorporated in the DID score followed two different patterns (figure 2): The progression in the domains "mobility without technical aid", "mobility with technical aid", "transfer", "changes of position" and "getting dressed" followed a hyperbolic function characterized by a steep initial increase to an asymptotically approached maximum value, while the scores for the domains "static body control", "eating and drinking" and "breathing" progressed exponentially indicating that these functions were severely affected late in the course. This may be related to the different types of muscles involved in these functions, as proximal skeletal muscles, which contain large muscle fibres, are affected early in the course of DMD, whereas muscles containing small calibre fibres are relatively spared initially, so that breathing and eating are more gradually impaired, a finding supported by animal models. [24,25]

Forced vital capacity (FVC), progressed with advancing age in accordance with our previous report and that of others. [5,6] Lung function rapidly deteriorated in young patients but declined less steeply thereafter (figure 3). Correspondingly, a more rapid yearly FVC decline of 8.5% was reported in DMD patients 10-20 years of age, whereas the decline was reduced to 6.2% per year above the age of 20 years. [26] It has been previously reported that DMD patients are more likely to develop chronic respiratory failure if their vital capacity falls below 1 L and the 5-year survival rate was only 8% if assisted ventilation was not provided. [27] In an early study, Brooke et al. [3] found that DMD patients passed this milestone at a median age of 13.5 years, whereas in the current study FVC was reduced to 1 L at a considerably higher age of 18.1 years. A possible explanation is the more general application of glucocorticosteroid therapy and other changes in treatment within the last two decades. [23] Unfortunately, there was no reliable information on previous glucocorticosteroid therapy available from our study cohort, thus we have not been able to explore the potential impact of this treatment on lung function. The less rapid reduction of FVC compared to earlier studies is unlikely related to the use of cough assist devices as our patients used such devices only during periods of increased mucus production (e.g. during chest infections). Half of our patients had less than 20 % of predicted FVC by the age of 20 years which corresponds approximately to the age at which assisted mechanical ventilation was initiated (on average 19.8 years). Similar to our findings, Toussaint et al. [6] reported a mean age of 19.4 years and FVC of 21 % predicted at the time of initiation of PPV.

The median survival of 35 years which we observed (figure 4) is considerably higher than the median survival of 14.4 to 20.5 years reported in patients not treated with assisted ventilation [27-29], and 26 to 33 years in patients receiving long-term mechanical ventilation. [6,30,31]. The probability of surviving 5 years after initiation of assisted ventilation was 70% in two studies analyzing this outcome. [6,32] In our cohort, the survival 5 and 10 years after beginning assisted mechanical ventilation was 82%, and 68%, respectively (figure 4). The recent improvement in survival of DMD patients may not only reflect advances in treatment but also the changing attitudes of care givers regarding various therapeutic options, e.g. therapy of cardiomyopathy, and spinal fusion surgery. [30]

In conclusion, our prospective longitudinal study provides novel data on the clinical course of DMD from childhood to adult life which updates and extends earlier cross-sectional observations. The DID score is a valuable instrument to describe the distinct patterns of disease progression in several domains of physical impairment and dependence on care. Our observations on clinical milestones and on the improved survival represent essential information for DMD patients, their families and caregivers as a basis for planning and evaluating care and therapeutic interventions.

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Figure legends

Figure 1:

DID scores obtained at yearly intervals in 43 patients (n=227 assessments). The age-related progressive limitation in activities of daily living and dependency on care is described by the function f=85.33*age/(10.05+age) and represented by the bold line. Thin lines connect data of individual patients.

Figure 2:

Trends of the 8 components of the yearly DID scores shown in figure 1 (n=227 assessments, 43 patients). Lines connect data of individual patients. A rapid progression in impairment with asymptotically approached maximal values in early life was noted in scores reflecting mobility, transfer, changing position and dressing. In contrast, the need for assistance in eating and drinking, breathing and static body control was modest in childhood but showed an accelerated increase in adulthood.

Figure 3:

FVC values progressively decreased with advancing age. Thin lines connect data of individual patients (n=170 assessments in 43 patients; the most severely disabled patients were unable to perform spirometry). The bold line represents an exponential decay function (f=139.1*exp(-0.08*age)).

Figure 4:

Upper panel: Kaplan-Meier curve showing the cumulative survival in 43 DMD patients.
Lower panel: Cumulative survival in 22 of the 43 patients following initiation of assisted positive pressure ventilation.

Appendix

The Duchenne muscular dystrophy physical impairment and dependence on care score (DID score)*

1.Mobility without technical aids	Points
Climbing stairs forward without help	1
Climbing stairs forward with help	2
Walking outdoors on uneven ground	3
Walking in the house, no carpet	4
Climbing stairs sideways with help	5
Walking with a rollator	6
Crawling on all fours, minimally 50 centimetres	7
Crawling on elbows, minimally 50 centimetres	8
Moving along the bedside, seated without help	9
Moving not possible without technical aids	10

2. Mobility with technical aids	
Biking	1
Biking with a special bike on even ground	2
Wheelchair driving, without motor, uneven ground	3
Wheelchair driving, without motor, even ground	4
Electro-wheelchair driving, without neck-stabilisator, every terrain	5
Electro-wheelchair driving, with orthopaedic aids, every terrain	6
Electro-wheelchair driving, with orthopaedic aids, every terrain, with help	7
Electro-wheelchair driving in cold weather with help	8
Electro-wheelchair driving, even ground, with help	9
Electro-wheelchair driving not possible	10

3. Transfer	
Transfer toilet to wheelchair without help, without sliding aid	2
Transfer chair to wheelchair without help, without sliding aid	4
Transfer chair to wheelchair without help, with sliding aid	6
Transfer chair to wheelchair with help, with sliding aid	8
Transfer chair to wheelchair only with lift / by lifting the patient	10

4. Changes of body position	
Standing up from the ground without help	1
Standing up from a chair without help	2
Standing up from a chair with help	3
Change from supine to seated position without help	4
Change from supine to prone-position without help	5
Change from supine to side-position without help	6
Change of position (supine) of the legs, arms and head without help	7
Change of position (supine) of the arms and head without help	8
Change of position (supine) of the head without help	9
Change of any position with help	10

5. Getting dressed	
Getting dressed fully without help	1
Getting dressed fully with help in organizing clothes	2

Getting dressed upper extremity, seated position without help	3
Getting dressed upper extremity, seated position, help lifting arms	4
Getting dressed upper extremity, seated position, help putting T-shirt into trousers	5
Getting dressed upper extremity, seated position, help closing a shirt	6
Getting dressed upper extremity, seated position, needs full help	7
Getting dressed in supine position	8
Getting dressed in supine position with care when changing body position	9
Getting dressed in supine position leads to dyspnea	10

6. Static body control

Standing on one leg without help	1
Standing on one leg with help	2
Standing on both legs without help	3
Standing on both legs with help	4
Standing on all four extremities without help	5
Sitting on the floor without help	6
Sitting on a chair without a lean / help	7
Sitting on a chair with a lean, head control without help	8
Sitting on a chair with leans for back, arms and head	9
Sitting with a corset or special seat	10

7. Eating and drinking

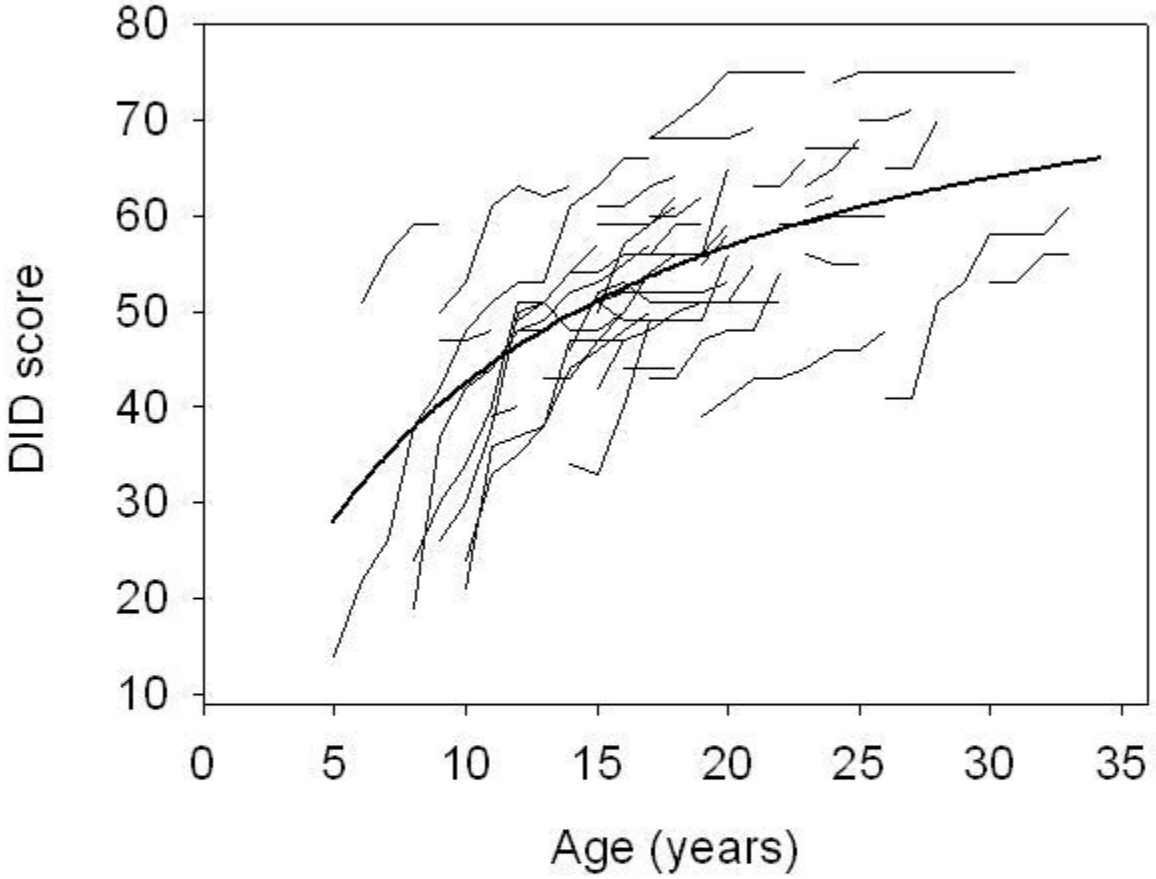
Eating at a table and preparing food without help	1
Eating at a table with fork and knife without help	2
Eating at a table with fork and knife with help	3
Eating at a table, meal can be transferred to the mouth without help	4
Meal must be given to the patient	5
Meal must be given to the patient, only in small pieces	6
Meal must be prepared especially for the needs of the patient	7
Meal must be supplemented with fluids	8
Compensating breathing movements while eating or eating only with NIPPV	9
Application of meals with tubes	10

8. Breathing

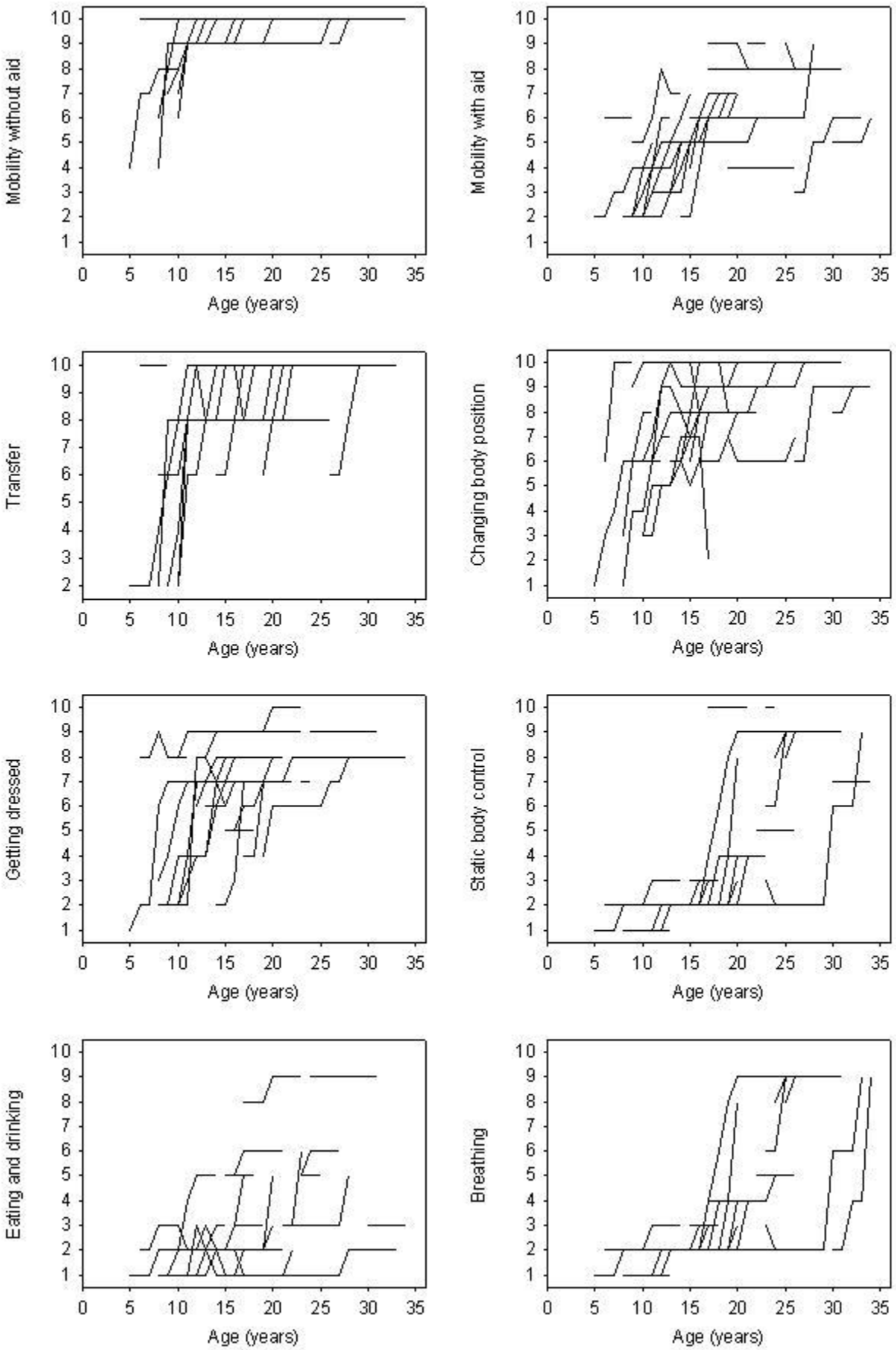
Normal breathing, normal vital capacity	1
Normal breathing, vital capacity reduced	2
Difficulty breathing, dyspnea when suffering from a cold	3
NIPPV during the night	4
NIPPV during the night, dyspnea when talking	5
NIPPV during the night, sometimes during the day for a few hours when dyspnoic	6
NIPPV during the night, during the day for more than 6 hours	7
NIPPV during the night, during the day for more than 9 hours	8
NIPPV during the night, during the day for more than 11 hours	9
Hypoventilation syndrome despite full time NIPPV	10

DID score (sum of domain scores)	**Range**
	9-80

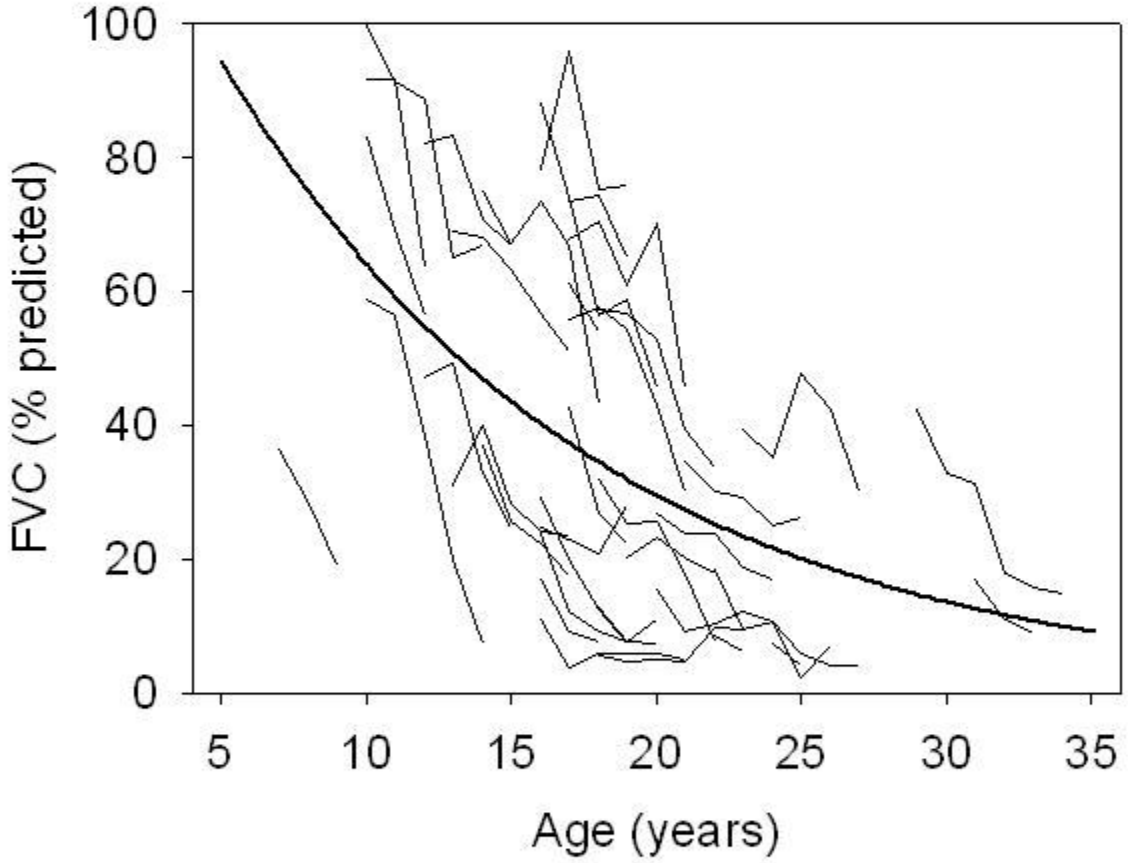
* The DID score is reproduced according to Kohler et al. [5]



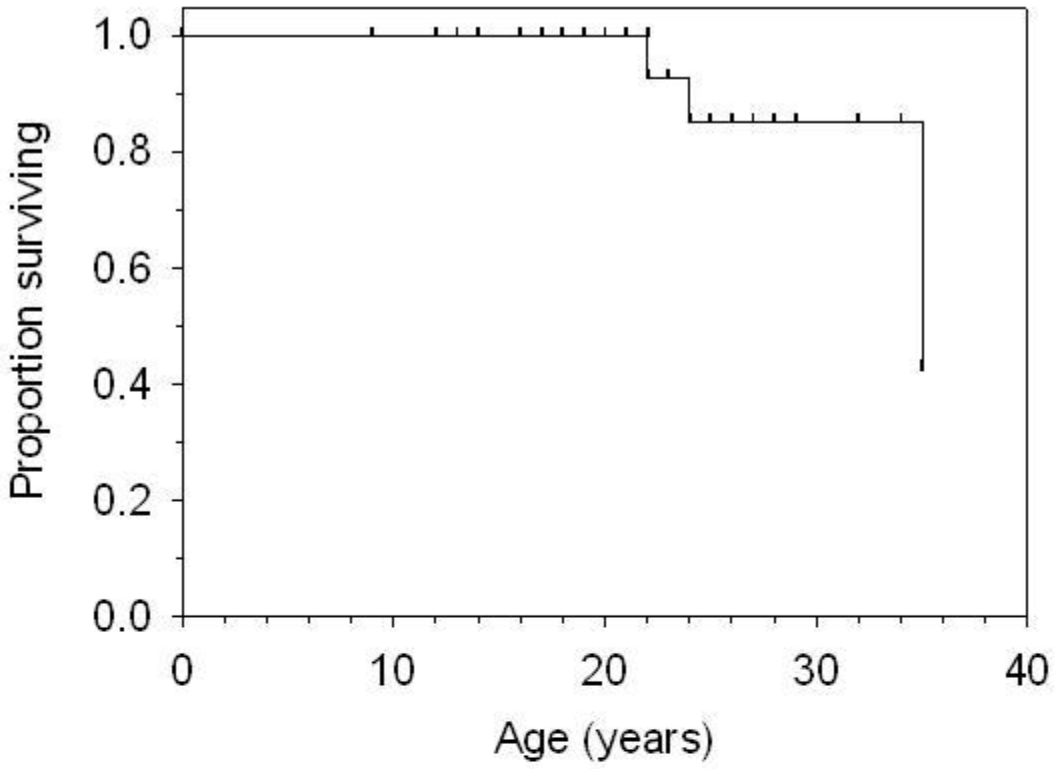
Kohler et al fig 1

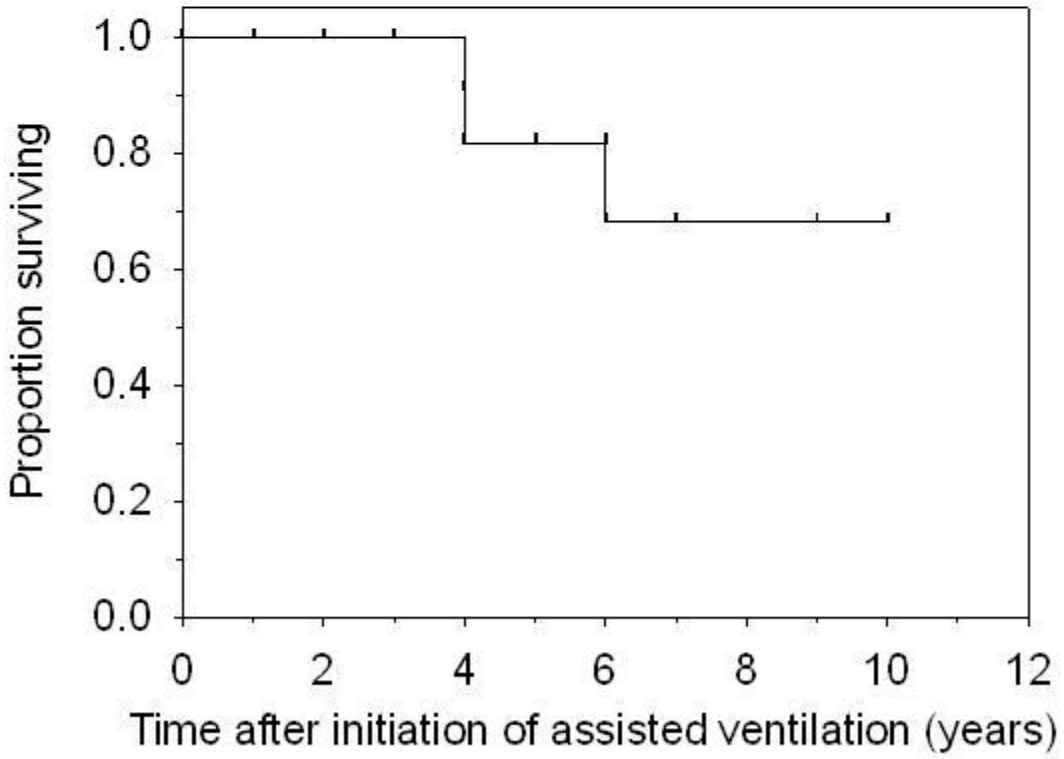


Kohler et al fig 2



Kohler et al fig 3





Kohler et al fig 4