Objective: To characterize the earliest symptoms of X-linked bulbospinal neuronopathy (Kennedy disease [KD]) during the course of the disease, including a definition of the age of onset.

Methods: We describe the earliest symptoms, signs on clinical investigation, electrophysiological and muscle biopsy specimen findings, and creatine kinase levels in 34 patients with KD. Correlations were made among the CAG-repeat length and clinical symptoms, age at onset, and the presence of electrophysiological and laboratory findings.

Results: Our findings indicate that the age at onset of KD is in adolescence which is earlier than previously thought. Most frequently early symptoms are gynecomastia, muscle pain, and premature muscular exhaustion. Weakness is not a typical initial symptom and is frequently found in distal limbs if present early. We found a correlation between the of number of CAG repeats and the age at onset of weakness but not to the age at onset of KD. Furthermore, no correlations were found between the occurrence of gynecomastia, tremor, increased creatine kinase levels, and additional myopathic changes in muscle biopsy specimens.

Conclusions: Our data show that KD is a multisystem disorder with onset in adolescence. Because of the heterogeneity of clinical presentation and no correlation between the number of CAG repeats and most of the clinical hallmarks of KD, we suggest that other environmental or genetic factors contribute to the manifestation of specific organ systems in KD.

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Since the first report in 1968 on a slowly progressive form of a X-linked spinal and bulbar muscular atrophy and the discovery of its molecular background in 1991, Kennedy disease (KD) has increasingly drawn attention.1,2 The disease is commonly described by slowly progressive proximal and bulbar weakness, muscular atrophy, ubiquitous fasciculations with predominance of facial muscles, and additional symptoms including gynecomastia (GM) and postural tremor. Kennedy disease is caused by an expansion of a polymorphic tandem CAG repeat in the first exon of the androgen receptor gene encoding a polyglutamine stretch.2,3 Some investigations described a weak correlation between age of onset of KD and the CAG-repeat length, with the onset of KD being described in the fourth to fifth decades of life.3,4 A 2001 publication reports a strictly defined border between normal and disease-causing alleles.5 Since clinical symptoms overlap with other neuromuscular disorders, for example, amyotrophic lateral sclerosis or spinal muscular atrophies, and clinical signs are nonspecific in early stages of the disease, KD was possibly misdiagnosed or underdiagnosed.6 After genetic testing became available, the number of case reports documented phenotypic variability.6,7 Even asymptomatic carriers of mutations have been described.8 Thus, the clinical diagnosis of KD may still be difficult. Defining the phenotypic spectrum of KD—in particular distribution of paresis, disease onset and characteristic symptoms—is, therefore important for the differential diagnosis, as it also is with regard to life expectancy, genetic counseling, and the increasing costs for diagnostic procedures, in particular genetic testing. Furthermore, for present and upcoming neuroprotective therapy studies, knowledge of the phenotype and identification of possible “markers” of early disease stages are relevant. There is ongoing discussion about whether CAG-repeat length influences clinical phenotype including onset and severity of typical and additional symptoms.

Most of the studies are limited by the small number of patients within the sample;

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only 2 reports included more than 20 patients. From 18 families we characterized 34 patients with genetically proven KD. We focused special attention on the earliest symptoms, definition of the age of onset, symptoms during the course of the disease, distribution of muscle weakness, abnormalities in muscle biopsy specimens, electrophysiological findings, and creatine kinase (CK) levels. Our analysis revealed that the onset of KD is commonly in adolescence, which is earlier than previously reported. Most frequently the early symptoms are GM, muscle pain, and premature muscular exhaustion. Paresis is not a typical initial symptom and, if present, is frequently found in distal limbs from early on.

**METHODS**

All patients were recruited from our neuromuscular outpatient clinic. They were asked for their medical history; detailed medical records were evaluated whenever available. The patients underwent standard clinical and routine laboratory examinations. Clinical findings were subdivided into 2 parts—the initial and actual symptoms. The age of onset of KD was estimated as the age at which first symptoms unequivocally related to KD became evident.

**ELECTROPHYSIOLOGICAL EXAMINATION**

Nerve conduction velocity studies followed standard techniques. Sensory nerve conduction studies were performed antidromically for the sural and radial nerve. Motor nerve conduction studies were done on the median and the tibial nerves at both sides. Electromyography was performed at 1 proximal and 1 distal muscle of at least 1 lower and upper extremity. Reference values were from our electrophysiological laboratory and are comparable to data in the literature.

Somatosensory evoked potentials (SSEPs) were obtained at the upper limbs by stimulation of the median nerve at the wrist and recording at the Erb point, above the spinothalamic tract C7, and on the scalp at C3 and C4. For the lower limbs, SSEPs were obtained by stimulation of the posterior tibial nerve at the ankle and recording of the spinal response at the L3 level and on the scalp at C2. For magnetic evoked motor potentials (MEPs) transcranial stimuli were delivered using a standard twin coil. The motor cortex of the hand or the foot area was stimulated and MEPs were recorded from the abductor pollicis brevis muscle and the adductor hallucis muscle bilaterally. Cortical latencies (CLs) were determined visually and the spinal latencies (SLs) were estimated by F-wave latencies following standard techniques. Central motor conduction time (CMT) was calculated by using the following equation:

\[
CMT = CL - \frac{[SL + (DML - 1)]}{2},
\]

where DML means distal motor latency. Reference values were from our electrophysiological laboratory and are comparable to data in literature.

**GENETIC ANALYSIS**

Genomic DNA was isolated from whole blood using standard techniques. Approximately 200 ng of DNA was used for a polymerase chain reaction to amplify a region of exon 1 of the androgen receptor—gene, including the CAG repeat of interest. One of the primers was labeled with fluorescent 6-FAM to enable fragment detection by a sequence analyzer (ABI310 Sequence-Analyzer; Applied Biosystems, Foster City, Calif). The length of the polymerase chain reaction products was ascertained using GeneScan software (Applied Biosystems). To calculate the number of repeats we cloned and sequenced, we used the polymerase chain reaction product of a reference and used this reference product in every single examination. To ensure reproducibility all experiments were done at least twice.

**LABORATORY ANALYSIS**

In all patients we attempted to get measurements of the CK, or glycohemoglobin or fasting morning blood glucose levels.

**STATISTICAL ANALYSIS**

Descriptive analyses were performed on clinical symptoms, CK levels, CAG-repeat length, and age. Correlations between CAG-repeat length and age of onset, onset of symptoms, or occurrence were determined using Pearson product moment correlation. *P* < .05 was considered statistically significant.

**RESULTS**

We examined 34 patients with genetically proven KD. Exact estimation of trinucleotide repeat numbers was done in 30 patients (Figure). In the remaining patients the genetic analysis revealed more than 40 CAG repeats. Nine apparently sporadic patients with a negative family history for KD were included in the study. In 25 patients exact data on first clinical features were available. In all individuals symptoms related to KD were found. The mean (SD) age at examination was 48.9 (8.1) years. Twenty-two individuals underwent detailed electrophysiological investigation. Symptoms at the time of investigation were heterogeneous and varied also between affected family members.
Diabetes mellitus was present in only 5 of 34 patients. The CK levels were elevated in all 18 cases investigated. Creatine kinase levels were documented during the first 2 years of onset of the disease in 8 patients and on actual investigation in 18 cases. Creatine kinase levels ranged between 111 and 1414 U/L (reference range up to 80 U/L). There were no relations between the age of onset of the disease, the duration of the disease, phenotypic variation, presence of a myopathic pattern in muscle biopsy specimens, and the level of CK. Patients with high CK levels retained high CK levels and the reverse was also true, that is, patients with low CK levels retained low CK levels during the course of the disease (data not shown).

Muscle biopsy specimens were evaluated in 11 patients (Table 1). In 4 patients a predominant neurogenic pattern and additional myopathic changes were documented. A predominant myopathic pattern was not found. There was no correlation between clinical symptoms, age of onset, CAG-repeat number, or progress of the disease and occurrence of myopathic changes in the muscle biopsy specimen.

Dysarthria often was only minimally seen despite the presence of tongue fibrillations, fasciculations, and atrophy indicating a remarkable mismatch between functional deficits and morphologic features of the tongue. Normally, bulbar involvement developed in an insidious way: sometimes augmented tickles of the throat, slight dysphagia, seldom attacks of shortness of breath, and nasal speech. Only a few patients started with obvious bulbar signs or an aggressive manifestation of dysarthria.

**DETAILED DESCRIPTION OF INITIAL FEATURES**

In 8 patients (34.8%), 2 or more simultaneously occurring symptoms were recollected (Table 2). The most common initial symptom was GM (52.2% of the patients). Some of these patients showed asymmetric GM and most of the patients who had GM had undergone mastectomy. In all of the patients undergoing mastectomy, GM re-

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**Table 1. Results of Muscle Biopsy Specimens and Electrophysiological Examination in Patients With Kennedy Disease**

<table>
<thead>
<tr>
<th>Patient No./ Age, y</th>
<th>No. of CAG Repeats</th>
<th>Muscle Biopsy Specimen Finding</th>
<th>SNAPS</th>
<th>CMAPs</th>
<th>SSEPs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Of Sural Nerve</td>
<td>Of Radial Nerve</td>
<td>Of Median Nerve</td>
</tr>
<tr>
<td>1/49</td>
<td>41</td>
<td>Mixed</td>
<td>Absent</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>2/43</td>
<td>50</td>
<td>Mixed</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>3/52</td>
<td>44</td>
<td>Mixed</td>
<td>Absent</td>
<td>↓</td>
<td>Normal</td>
</tr>
<tr>
<td>4/74</td>
<td>48</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>5/53</td>
<td>46</td>
<td>...</td>
<td>...</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>6/55</td>
<td>46</td>
<td>Mixed</td>
<td>↓</td>
<td>(↓)</td>
<td>Normal</td>
</tr>
<tr>
<td>7/48</td>
<td>50</td>
<td>Neurogenic</td>
<td>Absent</td>
<td>...</td>
<td>↓</td>
</tr>
</tbody>
</table>

*SNAPs indicates sensory nerve action potentials; CMAPs, compound muscle action potentials; SSEPs, somatosensory evoked potentials; MEPs, magnetic evoked motor potentials; MAPB, musculus abductor pollicis brevis; down arrow, decrease; ellipses, not applicable; up arrow, increase; parenthetical arrow, possible; and AP, amplitude.

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occurred later in life. In 5 patients with GM, detailed measurements of sexual hormone levels revealed no specific abnormalities (data not shown).

Nonspecific symptoms including premature muscular exhaustion (including muscles of mastication), exercise-induced or spontaneously occurring muscle cramps, and muscle pain were present in 43.5%. Further nonspecific symptoms were loss of efficiency, exhaustion (including difficulty of concentration), and the need for prolonged phases of recovery, an increased susceptibility for cold with a feeling of stiffness especially in distal muscles, and sleep disturbances because of a progressively reduced muscle tone of the pharyngeal muscles. In parallel with these early findings, we found 2 patients in whom elevated CK levels were documented long before the onset of pareses. A bilateral postural tremor of the hands often with emotional accentuation was observed in 26.0% as the initial symptom.

Only 2 patients had early paresis. One had a proximal paresis of the lower extremities; the other had bulbar involvement. Both patients were rapidly progressive with fast occurrence of generalized muscular atrophy of distal predominance within 2 years. Also, in these patients the extent of sensory disturbances in terms of an axonal peripheral neuropathy with distal symmetric hypesthesia and pallhypesthesia, infertility, and erectile dysfunction and the development of GM was extraordinary. On genetic analysis 1 patient had 50 and the other patient had 48 CAG repeats.

If the onset of the disease was determined by the first occurrence of initial symptoms as described earlier, we calculated a mean (SD) age of onset of 26.6 (12.6) years. There was a significant correlation between CAG-repeat length and the age of onset of pareses (r = -0.65; P < .01), but no correlation between the age of onset of KD and the number of CAG repeats (Figure 1). No statistically significant correlations were found between the number of CAG repeats and the age of onset of additional clinical symptoms and age of onset of GM, respectively.
tials were clearly abnormal in 4 of 16 patients investigated showing prolonged central motor conduction time.

The X-linked bulbohospital muscular atrophy (KD) is usually clinically distinguished from forms of spinal muscular atrophy, hereditary sensory and motor neuropathy, and amyotrophic lateral sclerosis by the pattern of inheritance and the typical clinical signs and symptoms due to androgen insensitivity. Early stages of the disease may be more difficult to diagnose and early symptoms (muscle cramps or premature exhaustion) may lead to misdiagnosis as myasthenia gravis, benign motor neuron disease, amyotrophic lateral sclerosis, limb-girdle and facioscapulohumeral muscular dystrophies, or hereditary neuropathy. We believe that our description of early disease stages in genotyped patients might help to identify these early disease stages. Previous studies focused on isolated or typical clinical features mostly in relation to the gene defect; and to our knowledge, there are only 3 publications analyzing clinical features in series with more than 20 patients.

Usually, the onset of paresis is determined as the onset of the KD. However, the symptom that describes the onset of the disease is inconsistently defined. Our investigations showed that there are symptoms years before these "typical" symptoms occur. If this symptom is seen as the onset of the disease, the mean age of onset was 2 decades earlier, that is, in the second to third decade of life. Thus, KD is not a disease of the second period of life, it is a slowly progressive disease starting at early adolescence.

We found that initial clinical findings were mainly GM (52.2%), nonspecific symptoms like premature exhaustion, muscle cramps, and muscle pain associated with motor neuron disease (43.5%), and more rarely a postural tremor (26%) (Table 2). In contrast to others, we found no correlation between the length of the CAG repeat and the age of onset of initial symptoms. These results may contribute to the current discussion on intrafamilial phenotypic variability in relation to the number of CAG repeats. An exact reason for the increased incidence for GM in our population that was even recurring after mastectomy is unknown. Tremor, often known as a "typical initial symptom," was found only in 26% of our patients at disease onset. In advanced stages of the disease consistent with previously published data, we saw a high-frequency postural and/or action tremor in 83.3% of the patients, occasionally with episodic occurrence. In our series, premature exhaustion and muscle cramps were a dominant symptom also in advanced stages of KD.

Paresis is not a typical initial symptom and we believe that the onset of paresis cannot be defined as the onset of KD. Mean age of onset of the paresis was in the third decade of life and most patients initially experience proximal muscle weakness of the lower extremities. This agrees with previous data. However, there is considerable variability, since one fifth of our patients started with an asymmetrical distribution of paresis and, even more remarkable, in our series a few patients recalled a paresis of distal muscles as an initial symptom.

Involvement of facial and bulbar musculature with fasciculations and atrophy is a common symptom of advanced stages. We saw 1 patient presenting bulbar symptoms early in the disease. The severity of the bulbar paresis ranged from mild to marked and was occasionally asymmetric. Facial fasciculations were mainly present at rest and prominent in the lower face. These findings are comparable to previous reports. For us, the remarkable mismatch between the extent of the tongue atrophy and the minor clinical signs of dysarthria and dysphagia are a clinical hallmark of KD.

Sensory impairment in KD as a clinical symptom was reported to be minimal or nonexistent. In contrast, there are electrophysiological reports on SSEPs and sensory neurography that document clear-cut axonal abnormalities. In our series we saw 50% of the patients presenting clinically with sensory impairment. Reduced or absent SNAPs were found in 81.8% of evaluated patients. Somatosensory evoked potentials of the posterior tibial nerve were clearly abnormal in 4 of 16 patients investigated by SSEPs and the minor clinical signs of dysarthria and dysphagia are a clinical hallmark of KD.

A relation between MEP findings and age, course of the disease, CAG-repeat length, or age of onset was not seen.

In all available muscle specimens, predominant neurogenic changes were documented. Further, in 4 patients additional signs of myopathy were detectable. It is unclear whether the myopathic changes are primary or secondary and what the possible relationship to the androgen receptor abnormalities at the muscle fiber level may be. Correlation between muscle biopsy specimen findings and CK level, number of CAG repeats, and/or severity of the disease were not found.

Our investigations clearly suggest that KD is a multisystem disorder beginning in puberty and early adolescence. We think that the traditional focus on motor abnormalities is an approach that is potentially misleading; this is particularly true for the correlation of the clinical picture and CAG-repeat number since a correlation between CAG-repeat length and most clinical features of KD is absent.

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Author contributions: Study concept and design (Drs Sperfeld, Schreiber, and Hanemann); acquisition of data (Drs Sperfeld, Karitzky, Brummer, Schreiber, Häussler, and Ludolph); analysis and interpretation of data (Drs Sperfeld, Karitzky, Brummer, Häussler, and Hanemann); drafting of the manuscript (Drs Sperfeld, Häussler, and Hanemann); critical revision of the manuscript for important in-
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