the distal myopathies, as for example, Nonaka myopathy, is ultimately a nonspecific histologic feature (45).

Miyoshi myopathy has recently been linked to chromosome 2p13; the gene has been cloned (61). The protein product of this gene has been called dysferlin (61a,61b); limb girdle muscular dystrophy (LGMD) type 2B has also been linked to this locus (62). Illarioshkin et al. (63) reported a large family in whom seven members had the typical LGMD clinical phenotype and three family members had distal myopathies. Both the LGMD and distal myopathy in this family were genetically linked to chromosome 2p13. The distal myopathy patients were different from the classic Miyoshi myopathy patients in that the anterior and posterior compartments of the legs were equally affected. Serum CK levels were elevated in both the LGMD and distal myopathy cases but more so in the patients with distal weakness, usually up to 56-fold normal. Muscle biopsy revealed nonspecific myopathic features, including autophagic vacuoles. Therefore, the clinical spectrum of chromosome 2p13 linked myopathies appears to be broad, and it is intriguing to speculate how different mutations in the chromosomal area and perhaps in the same gene give such disparate clinical phenotypes.

**LAING DISTAL MYOPATHY: EARLY ONSET TYPE 3**

Laing et al. (64) recently reported an Australian family of English/Welsh origin in which weakness begins in the anterior compartment of the legs and the neck flexors, followed by distal finger extensor involvement. Patients developed weakness between 4 and 25 years of age in an AD pattern. The serum CK was one to three times normal, and muscle biopsy showed moderate myopathic changes without vacuoles. The pedigree had nine affected members over four generations. The importance of this family is that genetic studies revealed linkage to chromosome 14. Although other cases with similar clinical features have not been described in the modern era, Laing et al. (64) believe their cases resemble the male patient Gowers described in 1902 (1). As previously mentioned, some authors believe the Gowers case may have had...
myotonic dystrophy (2,3,12). Whether or not the Gowers and Australian cases are the same disorder is primarily of historical interest and cannot be proven. However, these new cases are important because they provide us with another potential genetic region to explore in other distal myopathy patients. Hopefully, additional early adult-onset AD families will be reported to confirm the findings of Laing et al. (64). It is possible that the recent report of AD distal myopathy presenting in the first decade of life (65) and other early reports of childhood-onset distal myopathy may represent the same disorder (see below).

The genetic linkage of Miyoshi and Laing myopathies to 2p12-14 and 14, respectively, are important first steps toward a molecular understanding of these rare disorders. Until the genetic defects for the various distal muscular dystrophies have been discovered, we will need to continue to distinguish them based on their different clinical and laboratory features. The somewhat arbitrary nature of this type of classification is due to the overlapping clinical and histologic features. One can either lump all distal myopathies into one or two groups or split them into many categories. We have grouped them into six categories, the organization of which can expand or contract with subsequent understanding on a molecular level.

MYOFIBRILLAR MYOPATHY WITH ABNORMAL FOCI OF DESMIN

Another new category of distal myopathy has been proposed that is characterized by the pathologic finding of excessive desmin accumulation in muscle fibers (66–71). Desmin is not the only protein that accumulates in this disorder, and Nakano et al. (72) recommend the term “myofibrillar myopathy” because it may be a more accurate description of the spectrum of the pathogenic features. This was reported as desmin myopathy (73), desmin storage myopathy (74), spheroid body myopathy (75), cytoplasmic body myopathy (76), Mallory body myopathy and intermediate filament myopathy (77), familial cardiomyopathy with subsarcolemmal vermiciform deposits (78), and myopathy with intrasarcooplasmic accumulation of dense granulofilamentous material (79).

In addition, some cases previously diagnosed with other forms of distal myopathy probably had myofibrillar myopathy. Of note is the family by Horowitz and Schmalbruch (69) with myofibrillar myopathy that was reported earlier by Milhorat and Wolff in 1943 (9) as distal myopathy. The latter was considered to have Markesbery myopathy (11) until the desmin stains were performed.

The clinical features are to an extent heterogeneous, and it is unclear if myofibrillar myopathy is a distinct entity. There is a wide clinical spectrum in the myopathies associated with focal desmin accumulation (66), the manifestations of which are extensively reviewed elsewhere (68). Most patients develop weakness between age 25 and 45, although there are reports of onset in infancy and later in life. In the Scandinavian cases of Edström et al. (67), weakness began at about age 40 in the distal upper arms (Fig. 5). In other cases, the distal legs exhibited weakness first, usually in the anterior compartment (68,69). A scapuloperoneal pattern was reported in a large pedigree (69a). Most patients have an associated cardiomyopathy with heart block and arrhythmias, often requiring a pacemaker, and congestive heart failure. Progression to proximal muscles usually occurs, and some patients develop respiratory involvement requiring mechanical ventilation (69).

Some patients develop cardiac symptoms before skeletal muscle weakness occurs. Children as young as 1 year can have diffuse primarily proximal or distal weakness. Several pediatric cases have been described with a giant axonal neuropathy associated with a desmin in cardiac and skeletal muscle; the family of Muntoni et al. (70) with cardiac and respiratory involvement and distal weakness also had mental retardation (70).

Most pedigrees have shown AD transmission, although X-linked inheritance was suspected in one family (70). There are also reports of sporadic and AR inheritance (68). Desmin is encoded by a single gene at 2q35 (66). Recently cases have been linked to desmin gene mutations (79a,79b). In a large AD scapuloperoneal pedigree, linkage was demonstrated to chromosome 12 (69a). Further, in an autosomal dominant family with myofibrillar myopathy a missense mutation on chromosome 11q21–23 in the αB-crystallin chaperone gene was identified (79c).

Serum CK levels are modestly elevated, usually less than five times normal. EMG shows a myopathic pattern with complex repetitive, myotonic, or pseudomyotonic discharges. Muscle biopsy demonstrates variability in fiber size, fiber splitting, increased central nuclei, and increased

FIG. 5. Myofibrillar myopathy with abnormal foci of desmin. Note atrophy of the extensor forearm muscles.
connective tissue. Muscle fibers with rimmed vacuoles may also be evident. Subsarcolemmal cytoplasmic granular inclusions are seen, which are eosinophilic on hematoxylin and eosin stains and reddish or dark blue-green on the modified Gomori trichrome stain (Fig. 6A). In addition, dark-green smudges of amorphous material are also seen in Gomori trichrome stains (Fig. 6B). Immunohistochemistry reveals that these accumulations contain desmin (Fig. 6C). These deposits are amyloidogenic with Congo red staining (71). Excessive desmin accumulation has also been shown in cardiac muscles in patients with cardiomyopathy (70). Besides desmin, gelsolin, β-amloid precursor protein, dystrophin, and neural cell adhesion molecule are also overexpressed (80).

Electron microscopy demonstrates two major types of lesions: foci of myofibrillar destruction and hyaline structures that appear as spheroidal bodies (72). The foci of myofibrillar destruction consist of disrupted myofilaments, Z-disk-derived bodies, dappled dense structures of Z-disk origin, and streaming of the Z-disk (78). The spheroidal bodies are composed of compacted and degraded remnants of thick and thin filaments (72). Although some authorities have demonstrated the accumulation of 8- to 10-nm filaments (81), others have not found these intermediate-sized filaments despite extensive searching (72).

Desmin is an intermediate filament protein of skeletal, cardiac, and some smooth muscles cells (66). This cytoskeletal protein links Z-bands with the plasmalemma and the nucleus. Although it seems clear that some distal myopathy patients do have abnormal desmin deposits, desmin accumulation is a nonspecific finding and can be seen in a variety of neuromuscular conditions, including X-linked myotubular myopathy, congenital myotonic dystrophy, spinal muscular atrophy, nemaline rod disease, fetal myotubes, and in regenerating muscle fibers of any etiology (66,82). Therefore, we can tentatively add myofibrillar myopathy, with abnormal foci of desmin, to the distal myopathy category scheme, keeping in mind the above caveats. Perhaps other previously reported cases of distal myopathy with cardiac abnormalities (23,36) should be restudied for desmin accumulation. Desmin antibody is commercially available, and immunohistochemical staining should probably be done on muscle biopsy specimens from all distal myopathy. Only in this manner can we determine if the presence of desmin accumulation actually is a marker for a unique myopathic condition.

**FIG. 6.** Myofibrillary myopathy with abnormal foci of desmin. **A:** Focal granular cytoplasmic bodies and early vacuole formation (arrowhead) (modified trichrome, ×460). **B:** Dark green smudgy amorphous region (arrowhead) (modified trichrome, ×460). **C:** Focal nodular accumulations of desmin (immunofluorescence stain for desmin, ×800).
OTHER MYOPATHIES WITH DISTAL WEAKNESS

There are other myopathies that cause distal weakness; these are presented below and in Table 2.

Childhood-onset Distal Myopathy

There were early reports of infants that developed foot drop and finger/hand weakness before the age 2 years (83–85). This weakness was predominantly in ankle dorsiflexors, and wrist and finger extensor muscles, with AD transmission. Muscle biopsy and EMG supported a myopathic process but vacuoles were not seen. These cases remained either static after the teenage years or were very slowly progressive. All patients were ambulatory and quite active, and some were employed at work requiring extensive manual labor. The family recently described by Scoppetta et al. (65) can probably be placed in this clinical group.

One family with so-called juvenile-onset distal myopathy was also described (86). In this large Dutch pedigree, 19 members developed distal weakness in the hands and feet between ages 5 and 15 years. An AD inheritance was suspected. Both flexor and extensor distal muscle groups were affected. The disease progressed so slowly that the patients remained functional and active during adult life. Both myopathic and neuropathic features were seen on muscle biopsy and autopsy. These reports of childhood-onset distal myopathy preceded the availability of desmin staining, but there were no clues on light microscopy to suggest that excessive desmin may have been present. On the other hand, we mentioned earlier that the family described by Scoppetta et al. (65) had many clinical similarities to Laing myopathy. It is possible that these early reports of childhood-onset distal myopathy could represent cases of Laing myopathy.

Other Muscular Dystrophies

Weakness of distal muscle groups may be prominent in some forms of muscular dystrophy. In myotonic dystrophy, wrist and finger extensors and ankle dorsiflexors are typically weaker than proximal limb muscles, especially early in the disease (87). Because the prevalence of myotonic dystrophy is 5 per 100,000 (88), it is probably the most commonly seen myopathic condition with prominent distal weakness, especially in the young and middle-aged groups. Rare patients with the phenotypic appearance of myotonic dystrophy and distal weakness but without clinical or electrical myotonia have been described (89). Patients with fascioscapulohumeral (FSH) dystrophy can develop weakness of ankle dorsiflexion and wrist and finger extension along with typical facial and scapular muscle involvement. Rarely, they can present with ankle weakness (90). Indeed, the presence of foot dorsiflexor weakness is included in the diagnostic criteria for FSH dystrophy (91). FSH dystrophy has been mapped to chromosome 4q35 (92). Patients with the so-called myopathic form of the scapuloperoneal syndrome have significant ankle weakness (93). Now that we know the genetic localization of FSH dystrophy, it can be shown that some, but not all, patients with scapuloperoneal myopathy may be variants of FSH (94,95). Recently, a large family with a scapuloperoneal myopathy was found to have genetic linkage to chromosome 12 (96). Patients with the X-linked Emery-Dreifuss disease, also known as humeroperoneal muscular dystrophy, present with ankle dorsiflexion, triceps and biceps weakness, along with contraction at the elbow and ankle (97). Some pedigrees of oculopharyngeal muscular dystrophy also have significant distal extremity weakness (98–101).

Inflammatory Myopathies

Rare cases of polymyositis have been described in which patients first develop weakness of the hands and ankles (102,103). Biopsy of proximal muscles revealed an inflammatory myopathy, and patients improved with steroid therapy. A more frequent situation in which an inflammatory myopathy presents with early distal weakness occurs with sporadic cases of IBM (104–107). Sporadic IBM accounts for approximately a third of all cases of inflammatory myopathy and is probably the most common cause of distal weakness due to a myopathy in elderly patients. IBM patients develop slowly progressive weakness, usually after the age of 50. The slow evolution of the disease is one of the primary reasons for the delay in diagnosis, which averages approximately 6 years from

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**TABLE 2. Other myopathies that can have distal weakness**

<table>
<thead>
<tr>
<th>Childhood onset distal myopathy</th>
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<tr>
<td>Infantile onset (before age 2 yr)</td>
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<tr>
<td>Juvenile onset (before age 15 yr)</td>
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<tr>
<td>(? if these are Laing myopathy)</td>
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- Myotonic dystrophy
- Facioscapulohumeral dystrophy
- Scapuloperoneal myopathy
- Oculopharyngeal dystrophy
- Emery-Dreifuss humeroperoneal dystrophy
- Inflammatory myopathies
  - Inclusion body myositis
  - Polymyositis
- Metabolic myopathy
  - Debrancher deficiency
  - Acid-maltase deficiency
- Congenital myopathy
  - Nemaline myopathy
  - Central core myopathy
  - Centronuclear myopathy
- Nephropathic cystinosis
- Myasthenia gravis

*aScapuloperoneal distribution of weakness can occur.*