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MINI-SYMPOSIUM: Protein Aggregate Myopathies

Introduction

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Protein aggregate myopathies (PAMs) are a recently emerging group of neuromuscular conditions marked by aggregation of proteins within muscle fibers. They belong to the larger group of protein aggregate disorders (PADs), among which protein aggregate encephalopathies (PAEs) now form the major part of neurodegenerative diseases of the brain, such as Parkinson's and Alzheimer's diseases. Other central nervous system PADs include frontotemporal dementia affecting nerve cells, Alexander disease affecting astrocytes, as well as multiple system atrophy affecting oligodendrocytes. There is also a still small cohort of protein aggregate neuropathies (PANs) characterized by protein aggregation within axons and Schwann cells, with the foremost among these being giant axonal neuropathy. Other peripheral nerve diseases associated with enlargement of axons by excessive neurofilament assembly (Table 1) are further examples of PANs. In general, these PADs may be divided into hereditary and nonhereditary forms. Each of these types actually exists among PAM, PAE and PAN. Mutant proteins in PAD most likely initiate the aggregation of proteins in many hereditary forms, while the pathogenetic principles in acquired PAD are still enigmatic.

The concept of PAM originated from the demonstration of inclusions within muscle fibers, often seen in certain congenital myopathies (CMs). Hence, PAM, as hereditary forms, may be considered (clinically) as early or late-onset CMs, which themselves are defined by characteristic morphological lesions. Nemaline myopathy with aggregation of actin filaments owing to mutations in the *ACTA1* gene (5, 7), hyaline body myopathy owing to mutations in the *MYH7* gene (2, 11) or reducing body myopathy caused by mutations in the *FHL1* gene (6, 8) can now correctly be considered both CM and PAM. PAMs represent a luminous example of the heuristic principle "from the morphological substrate to the genetic defect," as, identifying an aggregated protein in the muscle fibers of a hereditary neuromuscular disease, initiated identification of its molecular and mutational background. This principle, for instance, was instrumental in carving out desminopathies, actinopathies and myosinopathies.

PAMs are a diverse group of conditions and may be divided according to the type of mutant protein primarily engaged in any hereditary PAM. Mutations in genes coding for certain sarcomeric proteins, that is, sarcomeric actin and myosin, and desmin, myotilin, filamin C and Z-band alternatively spliced PDZ motif-containing protein, in the summarily termed myofibrillar myopathies (MFMs) (3), give rise to protein aggregation—while sarcolemmal proteins are usually absent or reduced both immunohistochemically and by immunoblotting in certain muscular dystrophies, that is, dystrophinopathies and sarcoglycanopathies. In a halfway house, the combination of both absence of the sarcolemmal protein dysferlin and extracellular dysferlin aggregation caused by the same mutation in the dysferlin gene has recently been described (10). Mutations in the genes for chaperone proteins α-B crystallin and valosin may also result in respective PAM, α-B crystallinopathy and valosinopathy; the latter also affecting neurons by intracytoplasmic and intranuclear valosin-containing inclusions, thus representing a rare example of combined PAM and PAE.

The current nosological state of MFM will be presented by Benedikt Schoser and Rolf Schröder in this issue. As MFMs are primarily defined by myopathological criteria, larger cohorts (9) include only a fraction of conditions with identified mutant genes. Other patients/conditions remain familial without identified mutations, or "sporadic," that is, they are caused by *de novo* mutations, or they are truly nongenetic, that is, acquired. However, individually acquired MFM may not even be correctly ascertained by exclusion of mutations in known genes as mutations in unknown genes cannot be ruled out. Inclusion body myositis (IBM) is the major nongenetic PAM affecting, like many other PAMs, individuals in later life. In IBM and other nongenetic PAMs, a multitude of proteins accrue, but the decisive "initiator" protein remains a matter of

speculation. In IBM, amyloid-associated proteins of beta and prion types accrue within muscle fibers—contrary to their accumulation in the extracellular space of the cerebrum in PAE. IBM, thus being the exemplary acquired PAM, will be discussed by Valerie Askanas and coworkers.

There is growing evidence that extralysosomal degradation of proteins within muscle fibers fails in PAM. This extralysosomal protein degradation points at the ubiquitin–proteasome (UP) pathway, and one of the issues is whether protein aggregation overwhelms the UP system and whether this takes place in hereditary forms of PAM or whether primary failure of the UP system induces protein aggregation perhaps in acquired PAM. This aspect will be addressed by Montse Olivé. However, while PAM of later age may stem from impaired extralysosomal protein degradation, a catabolic failure in certain hereditary PAM, other PAMs more often occurring in childhood, such as actinopathy in particular and myosinopathy to a lesser degree, may represent diseases of anabolic or intracellular maldevelopmental or dys-synthetic processes. These "anabolic" PAM will be canvassed by Hans Goebel and Nigel Laing.

MFM and certain early childhood PAM, as well as IBM, form the majority of PAM. Protein aggregation within nuclei and sarcoplasm of myofibers may also be encountered in trinucleotide repeat disorders, such as oculopharyngeal muscular dystrophy and bulbospinal muscular atrophy, again paralleling trinucleotide repeat disorders of the brain.

Amyloidoses of the nervous system, both the brain and the peripheral nervous system, when comprising hereditary forms involving amyloid plaque formation in the brain in Alzheimer and related diseases, and transthyretin or gelsolin aggregation in the PNS, are examples of PADs with extracellular protein aggregation. Amyloidoses owing to formation of abnormal immunoglobulins in plasma cell dyscrasias are usually not considered PAD of degenerative nature.

A list of currently recognized PAMs is given in Table 2.

Table 1. Protein aggregate neuropathies.

Hereditary	Acquired
Giant axonal neuropathy 16q24.1; GANI/gigaxonin	B12 deficiency
Autosomal-dominant neuropathy with cardiomyopathy—HMSN II type (4, 12)	Amyloidosis
Porphyria	Industrial solvents
Neuromyopathy and cardiomyopathy with desmin storage (1)	*n*-hexane—glue sniffing
	Methyl-*n*-butyl ketone—(MBK)
	2.5-Hexanedione
	Acrylamide
	Disulfiram
	Vincristine
	Cisplatinum
	Colchicine
	Podophyllin
	Iminodiproprionitrile
	Carbon disulfide
	Misonidazole

Table 2. Protein aggregate myopathies.

Catabolic:
Desminopathy
α-B crystallinopathy
Myotilinopathy
ZASPopathy
(Z-band alternatively spliced PDZ-containing protein)
Selenoproteinopathy
C-filaminopathy
BAG3opathy
(Bcl-2-associated athanogene-3)
Valosin-containing proteinopathy
Lamin(A/C)opathy
Other myofibrillar myopathies
2q21 Myopathy
10q23 Myopathy
15q22 Core-rod-desmin (CRD) Myopathy
Core diseases
Cap disease
Ragged red fiber diseases
Sporadic & hereditary inclusion body myopathies (s & h-IBM)
Other myopathies marked by inclusions (putative), for example,
Reducing body myopathy
Oculopharyngeal muscular dystrophy
Anabolic:
Actinopathy
Myosinopathy (Hyaline body myopathy)

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