Critical Care Myopathy: an Emerging Medical Catastrophe

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Whereas the advent of intensive care units (ICU) in the 1950s resulted in improved survival of critically ill patients, a variety of new clinical disorders emerged related to prolonged ICU stays and the complications arising thereof. Critical care myopathy is one such disorder and has fast become one of the commonest acquired neuromuscular disorders.' The disorder was first recognized in 1978 by MacFarlane et al. in their patients with status asthmaticus who required mechanical ventilation and were treated with high dose corticosteroids.- Since this original description, there have been many reports from all over the world.[3,4] The incidence of this myopathy also seems to be higher in patients receiving bone marrow or solid organ transplantation.[3,5-e]

Scope of the Problem

Most reports on this myopathy are retrospective and the incidence figures range from 7% to as high as 90%.[1] De Jonghe and colleagues prospectively followed patients in three medical and two surgical ICUs at 4 medical centers in France and found the incidence rate for critical care myopathy of 25%.[9] In the US the additional economic burden created by this myopathy is estimated to be $66,000 per patient.'°

In addition to the short term morbidity and mortality, the long term morbidity associated with this myopathy is also very high.[11] Herridge et al. followed a cohort of 109 survivors of acute respiratory distress over a 1 year period; these patients had all survived severe critical illness (median APACHE score of 23).[11] They found significant neuromuscular weakness (distance covered in a six minute walk) at 3-, 6- and 12- months following discharge compared to predicted values. The absence of systemic corticosteroid treatment, the absence of illness acquired during the intensive care unit stay, and rapid resolution of lung injury and multiorgan dysfunction were associated with better functional status during the one-year follow-up.[i]

Clinical Description

This syndrome is characterized by sub-acute onset of flaccid weakness and respiratory failure.[3] Typical course is development of muscle weakness over days to weeks. The muscle weakness may be variable and ranges from mild weakness to severe quadriplegia."- The muscle weakness follows a typical pattern of proximal greater than distal weakness, but diffuse muscle weakness may be seen.' Facial muscle weakness is common but the extraocular muscles are often spared. Sensory dysfunction is uncommon but is difficult to ascertain due to difficulty with communication with paralyzed intubated patients. A length-dependent polyneuropathy often co-exists in majority of the patients."M[3] Deep tendon reflexes are often depressed, even in patients with no electrodiagnostic evidence of neuropathy. This leads to clinical confusion between myopathy versus neuropathy.[9,13]

Respiratory insufficiency is invariable in severe cases, and failure to wean from mechanical ventilation is often the initial manifestation.[1,3] Since most of these cases are associated with prolonged neuromuscular blockade=', the presence of prolonged paralysis from persistent neuromuscular blockade needs to be ruled out.

Laboratory Investigations

CPK levels may not be elevated. except in cases where a neuromuscular blockade-related rhabdomyolysis may have occurred.' Renal insufficiency may be present in some cases.' The diagnosis is usually based on clinical suspicion, confirmed by electrodiagnostic studies and muscle biopsy.

Electrodiagnostic studies are fraught with technical issues related to ICU related electrical artifacts.[1,14] Motor nerve conduction studies often show reduced compound muscle action potential amplitudes (CMAPs); conduction velocities and distal latencies are not affected.[15] Sensory potentials may be difficult to record in the ICU setting, they may be reduced or absent in a length-dependent fashion. In acute cases, especially with severe muscle weakness, the nerve conduction studies may not elicit much response due to muscle membrane inexcitability.[16-1"] Needle EMG examination shows increased spontaneous activity with variable degree of fibrillation potentials.[3,14] Motor unit analysis shows evidence for a myopathy, with typical short duration potentials with early recruitment.[15,is] Motor units analysis may not be possible if the patient is too weak to generate motor units. This has resulted in an increased confusion on how to accurately interpret the length-dependent sensory potential abnormalities and the needle EMG evidence of "denervation" and thus it is not unusual for the patient to be labeled to have "critical care neuropathy".[19] Repetitive nerve stimulation is an important component of

the electrodiagnostic study to rule out prolonged phannacoloaic neuromuscular blockade or to diagnose rare cases of sub-clinical myasthenia gravis.

The ultimate diagnostic resource is a muscle biopsy and the importance of pathological studies was emphasized recently by De Jonglie et al 9 Figure shows the typical features of this myopathy. Muscle fiber atrophy is often severe; the atrophy tends to affect fast type 11 fibers more than slow type 1 fdbers.i,[3] Muscle fiber necrosis occurs in some cases, especially those associated with rhabdomyolysis.i The hallmark *of* this myopathy is the loss of myosin heavy chain, appreciated best on myosin-ATPasc stains as well as on electron microscopy. 3,4,6 The myosin heavy chain loss may be patchy and often may occur focally -- 'thin a muscle fiber.'

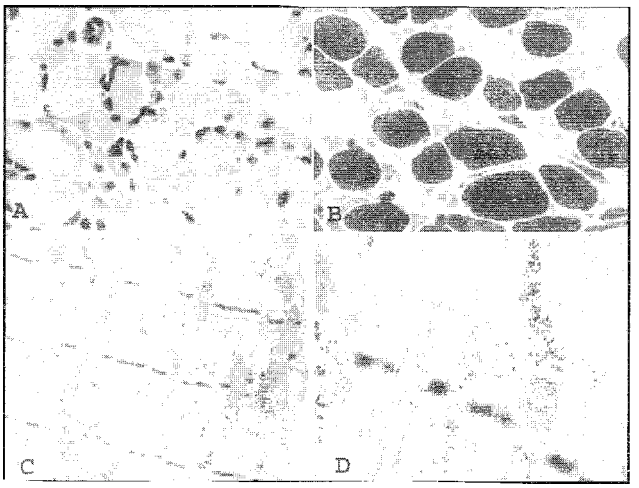

Figure. Specific myopadtoiogical features in critical ctve nn°opathy with selective myosin heave chain depletion. Panel A and B show muscle padtologn in a 10 sear old boy tt'ith severe muscle ,,eaknesss and ventilator-dependence follo,im, treatment for status assthmaticus- A. X1orpholo~ical stains show inane (dark) atrophic libels (N&E X600)_ B. Enzyme histocheinistrv show many fibers with absent myosin-,V1Paso staininf. Normally at this alkaline stain two fiber types are seen; dark fibers are type il and intermediate ntv in e type I fibers. :1 third population of libecs with no ATPasc stain' -, such as seen here_ is the hallmark of this disordei (\lyosin-ATP aye 9-1 X600)_ C. Electron microscope of muscle fibers fron a 67 tear old woman who was quadriplegic and ventilator d pendent after a ,tons c Curse in the lCh after sinll ho -1 perforation. l1vofbrillar di array and scvero depletion, of mvo in heavy chain i, obvious ?Fore the Pe. ·s stenec of Z-discs but severe disnption of the iJ-hand:. \°_H,80n. D ili,h Power of electron microscope image fom C. Please role if,, severe loss of myosin hemv chains, acts filaments can still he seen altlwu;n tic_,; are probably also reduced Some. Xd-.000.

Predisposing Factors

Critical illness. sepsis, organ transplantation, multiorgan dysfunction, use of glucocorticoids and pharmacologic neuromuscular blockade are risk factors for development of this myopathy.] The association with pharmacologic neuromuscular blockade and administration of high dose glucocorticoids is well establislied. 4,6-'-0 De Jonghe et al.in their multivariate analysis found a very strong association with corticosteroids in the development *of* this myopathy (odd ratio 14.9; P<0.01).[9] Their other independent risk factors included female sex, duration *of* mechanical ventilation and presence of organ dysfunction in two or more organs.`

Role of denervation is important given the association of this myopathy with pharmacologic neuromuscular blockade (functional denervation).% A length-dependent neuropathy co-exists in a majority *of* these patients.? The role of denervation, whether due to axon loss or due to functional denervation from neuromuscular blockade, towards development of this myopathy has not been studied systematically, but has been hinted at by De Jorighe and colleagues.`% An important clue towards the role of denervation in causing this myopathy conies from anecdotal report from the critical care unit at the Aga i,.han University, in Karachi, Pakistan, showing decrease in incidence of ICU]-related quadriparesis with rede!ction in the use of non-depolarizing neuromuscular blocking agents, such as Pancuronium, Vecuroniurn, etc (Sardar ijlal Babar, personal communication). it is however, possible that the mvopathk may be related to a unique deleterious effect of glucocorticoids on skeletal muscle disuse related to denervation or critical illness and not specifically to the effects of denervation.

Critical=, irh3ess seems to be a prerequisite for ndvosin heavy chain caepletion.l However, myosin heavy chair: loss is not specific to critical care myopathy and can be seer foc< in a variety of disorders, includino derntaton vosir s -Inct thrombotic thrornbocytopenic purpura.=! Myosidi depletion (critical care) myopathy can develop ini the absence: ol any known use of non-depolarizing neuromuscular b ockkade to glucocorticoids.-= This emphasizes the role of critical dine and the associated physiolo,izical changes, sucli as SelzSiS-- i; development *of* this myopathy. Cpre~`ulatior d`ulatiord o1_ c,rtol:ines. both pro- and anti- inflammatory..have been reported fhom human muscle samples from these patients. -

Pathophysiology

Glucocorticoids have well established negative effects on skeletal muscle protein synthesis and protend, degradation.=3,24 GILIcocorticoids cause il]CFeased protelr1 breakdown and this mechanism is considered _ o Oe lie wain effector f0:1 glucocorticoid-'Indt7ced skeletal nuscle atrophy."-"'s Upregulation of the traditional markers of protein degradation, such as ubiquitin-proteosotnal proteri~~. and calpain family *of* proteases, has beet, shown to be upregulated in critical care myopathy.f==6 Such catabolic markers may explain the enhanced muscle atrophy in this disease but do not satisfactorily explain the selective myosin heavy chain depletion. Recently two 1lluscle specific ubiquitin-c.3 ligases. MURF-1 and Atro`;in-1, have heel; described.'-7-2s Messenger RNA (rnRNA) for these proteilrs is upregulated in skeletal muscle atrophy from ant cailw c, including denervation and glucocorticoids.=· -` Furthernioi there is experimental evidence to suggest tha these may be translocated to the mvonuclei where they :3; cause proteolysis *of* crucial muscle transcription taetok.~. further aggravating muscle atrophy.'`) MURF-l has also b;;~rz

shown to have glucocorticoid responsive elements, and this combined with its crucial localization to the M-band and its known interaction with myofibrillar proteins [30], may explain the selective rnyosin heavy chain depletion in this myopathy.

Glucocorticoids are known to decrease production and signaling of Insulin-Like Growth Factor-I (IGF-1)[31]; other actions include suppression of IGF-I regulated protein synthesis.[31] IGF-I is known to down regulate protein breakdown and has anti-apoptotic effects on muscle cells.[33] The contribution of glucocorticoid-induced suppression of protein synthesis or other critical pathways in muscles, such as IGF-I signaling, has not been studied in this disease so far.

Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes.[34] Insulin resistance is known to occur in denervated muscles; denervated muscles show decreased insulin-stimulated glucose transport and protein synthesis, both related to impaired AKT-a activation, air important mediator of cellular functions related to insulin and IGF-I signaling.[35] Van Den Berghe recently, by maintaining blood sugars between 80-110 mg/dL through intensive insulin therapy, showed that normalization of blood glucose levels with insulin therapy improves prognosis by halving the mortality rates in critically ill patients 34. An impressive 44% reduction in the incidence of critical care myopathy was partly responsible for reduction in the inortality.[34]

The contribution of a denervative substrate towards the development of this myopathy is at best speculative at this stage.` Denervation reduces protein synthesis and enhances protein breakdown through similar pathways as glucocorticoids.[36,37] Denervated muscles show upregulation of nicotinic acetylcholine receptors and show increase sensitivity to the effects of neuromuscular blockade.[38,39] Glucocorticoid receptors are also upregulated in denervated inuscles[40] (as well as muscles from septic animals)[41] and thus these denervated muscles may be more sensitive to the effects of exogenous corticosteroids.

Myonuclear apoptosis (non-necrotic programmed cell death) may also play a role in this disease. Skeletal muscles from patients with critical care myopathy show evidence of apoptosis.[42] A recent DNA microarray study showed upregulation of cellular pathways concerned with nuclear apoptosis in human skeletal muscles from such patients (Di Giovanni S, Hoffman EP, et al.; personal communication). Denervated muscles are known to have enhanced myonuclear as well as satellite cell apoptosis[43] and glucocorticoids are known to induce skeletal muscle apoptosis through suppression of IGF-1 mediated AKT pathways.[31]

Treatment

Treatment regimens in this myopathy presently consist of aggressive physical therapy, withdrawal of corticosteroids (if possible), and reduction of non-depolarizing neuromuscular pharmacologic blockade. No systemic trials of any pharmacologic treatment regimens have been studied. Similarly the role of aggressive physical therapy or other modalities to keep muscles active has not been studied. Authors' personal experience suggests possible benefits of anabolic steroids such as oxandrolone but this has not been systematically studied. Intensive insulin therapy as described above has been shown to reduce the incidence of this myopathy by 44% and should be employed more frequently.[34] A better understanding of the molecular mechanisms underlying this myopathy would lead to better molecular and pharmacologic treatment of this myopathy.

Prognosis

The morbidity and mortality in this disease is very high[10,11] but can be minimized with proper intensive care. It is important to recognize that this myopathy is reversible with complete recovery of muscle atrophy, myosin neavy chain loss and reversal of muscle membrane inexcitability.' This recovery may take weeks to months and it is important to aggressively treat patients and minimize predisposing factors such as neuromuscular blockade and corticosteroid use to ensure survival,

Future Research Directions

There are many unanswered questions in this myopathy; the role of denervation and glucocorticoids or the role of a systemic inflammatory response (SIRS; has not been satisfactorily studied. Similarly the role of IGF-1 and other such trophic factors has not been studied. Part of the reason why there has been a lack of progress in understanding this myopathy has been the reluctance of critical care physicians to subject their already sick patients to further invasive studies, such as muscle biopsy.

Fortunately an animal model of this myopathy was described in 1987[14] and much work has already been done in fiirther cliaracterization ofthis iriodel.[45-47] Much ofthe earlier work on this rodent model has concentrated on understanding the =molecular basis of the muscle membrane inexcitability but the focus has lately changed to also understand the molecular mechanisms underlying muscle atrophy and selective myosin heavy chain depletion.[48,49] 'These studies will hopefully answer some of the unanswered questions and assess treatment strategies.

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