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Short Communication

Serum Creatine Kinase in Patients with Neuromyelitis Optica Spectrum Disorder

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ABSTRACT

Objectives: There have been reports of elevated serum creatine kinase (CK) and myopathy in patients with Neuromyelitis Optica Spectrum Disorder (NMOSD). Such findings have raised the possibility that myopathies may be a part of the spectrum of NMOSD. The incidence of elevated CK in NMOSD remains unknown. We sought to assess the potential association between hyperCKemia, myopathy, and NMOSD, and the potential role of screening for muscle involvement using serum CK.

Methods: We reviewed records of all aquaporin 4 (AQP4) antibody-seropositive and seronegative NMOSD patients who had CK levels evaluated at two major academic medical centers.

Results: Of 199 total NMOSD patients, CK levels were checked in 43, and elevated, on at least one occasion, in 4. In 1 patient, CK was elevated during an NMO exacerbation. A myopathic process occurring with NMOSD was suggested in 2 of 4 patients in the form of symptomatic complaint of myalgias and associated MRI signal change.

Discussion: Unexplained hyperCKemia was found on one or more occasion in 4 of 43 tested NMOSD patients. Testing NMOSD patients for serum CK may reveal otherwise unsuspected myopathy. More formally powered, prospective assessment of the incidence and utility of CK in NMOSD is needed.

1. Introduction

Muscle involvement in NMOSD has been documented in multiple reports, summarized in a recent review (He et al., 2017). Routine laboratory testing (Deguchi et al., 2012) or testing done in the presence of myalgias (Okada et al., 2013) sometimes reveals hyperCKemia in such patients. In a review of 773 patients with NMOSD, 3 had very high CK levels (ranging from about 69.5 to 331 times the upper normal level), with all 3 having generalized fatigue and one having muscle pain. Development of additional neurological symptoms led to the ultimate diagnosis of NMOSD and the association between hyperCKemia and NMOSD (Suzuki et al., 2010).

No temporal association has been well established between hyperCKemia and the diagnosis of NMOSD or aquaporin 4 (AQP-4) antibody seropositivity, with hyperCKemia often preceding the diagnosis of NMOSD (Deguchi et al., 2012; Okada et al., 2013; Suzuki et al., 2010). Another group reported hyperCKemia to also be present with subsequent central nervous system (CNS) flare-up (Deguchi et al., 2012). More recently, an observational study reported a relative elevation of CK level during NMO exacerbation. The authors compared mean log serum CK levels of NMOSD patients in the acute and stable phases and found that they were higher in the former (Chen et al., 2017).

AQP4 is expressed in the sarcolemma of fast-twitch skeletal muscle fibers in rats (Frigeri et al., 1998). It is also found in the sarcolemma of quadriceps muscle from human controls showing normal histology (Frigeri et al., 2002). Interestingly, reduced AQP4 mRNA has been reported in Duchenne muscular dystrophy as well (Frigeri et al., 2002; Wakayama et al., 2002). Muscle expression of AQP4 expression was also shown to be reduced in patients with amyotrophic lateral sclerosis (Jimi et al., 2004).

The question remains, 'How commonly is muscle involved in NMOSD?' Furthermore, 'Is routine serum CK level screening useful in NMOSD patients not having overt myopathic features?'

2. Methods

We undertook a retrospective review from 2000 to 2017, including NMOSD patients who were either AQP4 seropositive or seronegative but who met the 2015 diagnostic criteria (Wingerchuk et al., 2015). We obtained and reviewed records of all AQP4 seropositive patients as well as those carrying a discharge diagnosis of 'NMO', 'NMOSD', 'transverse

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myelitis (TM)', 'myelitis', 'partial transverse myelitis', 'non-compressive myelopathy', 'optic neuritis', 'optic neuropathy' and 'multiple sclerosis' at the Detroit Medical Center/Wayne State University and The Ohio State University Wexner Medical Center. Expedited IRB approval was obtained at both institutions.

Charts were screened and included only if a diagnosis of NMOSD was met, be it AQP4 antibody seropositive or seronegative, and if CK levels were tested at any point in time. Myelin oligodendrocyte protein (MOG) testing was not performed in any of these individuals. For CK normal reference values, we followed the institutionally adopted laboratory guidelines. Additional key data was also gathered, namely race, gender, other potential myopathic confounders (e.g. myocardial infarction or unstable angina, statin use, trauma, seizure, hypothyroidism), as well as immunosuppressant use (Jaffe et al., 1984; Dillon et al., 1982; Ay et al., 2002; Beyer et al., 1998). If any confounders were present, those patients were eliminated from analysis. In addition, we assessed the indication for CK level testing in those patients.

3. Results

119 total NMOSD patients were identified, 43 having had CK level tested. Of those 43, 30 were AQP4 seropositive, 12 seronegative, and 1 of unknown antibody status. Ultimately, CK was elevated in 4 patients in whom no other conditions or causes of elevated serum CK could be identified. Of note, 1 of the 4 was AQP4 seronegative (Table 1). Patient #1 had marked hyperCKemia (1225) during a presenting episode of paraplegic C6 transverse myelitis. Patient #3 also had a significant CK elevation of 7357 with MRI report of nonspecific signal change in mid-thoracic paraspinal muscles suggestive of myopathic injury. Unfortunately those images are no longer available. Patient #2 had modest CK elevation (497) and was tested for an unclear reason. Patient #4 had modest CK elevation in the setting of symptomatic complaint of myalgias but no imaging or other testing was performed to confirm muscle involvement. Of note, 3 of the 4 patients with hyperCKemia were on some form of immunosuppression at the time of their documented CK elevation as detailed in Table 1.

No consistent indication for CK testing could be identified in the 43 patients, including the 4 with documented hyperCKemia. In most, CK level was obtained as part of the basic metabolic profile on admission or in clinic. In a few instances, CK was ordered because of symptoms of myalgias, particularly in patients taking statins as well as those with concomitant myasthenia gravis, rhabdomyolysis, or weakness. Checking CK levels during NMOSD exacerbation, as with patient 1, was uncommon. No electromyographic data were available on our four identified patients with idiopathic hyperCKemia.

4. Discussion

The association between NMOSD and hyperCKemia remains difficult to establish as CK levels are infrequently, if ever, routinely measured in NMOSD patients. In our study, 4 of 43 NMOSD patients were found to have significant idiopathic hyperCKemia. A recent study documented NMOSD-associated myopathy in 12 cases (He et al., 2016). Muscle disease in those NMOSD patients was characterized by marked CK elevation in the setting of only mild muscle symptoms, prompting the authors to speculate that CK leakage rather than muscle necrosis was the predominant underlying process. In our patients, a similar mechanism is certainly possible. Of note, hyperCKemia can also be detected in several CNS disorders including stroke, but even then, still shows an MM pattern on isozyme analysis, thus suggesting muscle as the source (Ay et al., 2002; Bayer et al., 1976; Lisak and Graig, 1967).

Similarly, one wonders whether a pure "neurogenic" etiology may play a role in hyperCKemia in NMOSD patients such as can be seen in spinal cord injury and amyotrophic lateral sclerosis. However, pertaining to spinal cord injury, one of the largest series showed that the majority of patients with chronic spinal cord injury had CK levels

Table 1
NMOSD patients with hyperCKemia. Normal range of CK: For patients #1 and #2 (30–186 U/L), for patient #3 (25–240 U/L), and for patient #4 (35–350 U/L). NMOSD, Neuromyelitis Optica Spectrum Disorder; CK, Creatine Kinase; W, White; AA, African American.

#	Age	Sex	Race	Year of Diagnosis	Antibody status	CK (year)	Indication/muscle symptoms	Treatment (year)	CK after Treatment
1	28	M	W	2005	Negative	1225 (2005)	Weakness in the setting of C6 transvers myelitis	Plasma exchange after CK testing	Not available
2	29	M	AA	1993	Positive	497 (2005)	Unknown	Azathioprine and monthly intravenous methylprednisolone (2004)	113
3	12	F	AA	2011	Positive	7357 (2012)	Myalgia	Rituximab (2011)	95
4	38	M	AA	2014	Positive	526 (2014)	Myalgia	Mycophenolate Mofetil (2014) Rituximab (2016)	112

within 95% of able-bodied individuals. (Szlachcic et al., 2002). With regards to ALS, a known neurogenic cause of hyperCKemia, multiple studies have shown median or mean CK levels to range from only 117–240 U/L (Tai et al., 2017; Harrington et al., 1983).

Establishing a correlation between hyperCKemia and muscle histology remains particularly elusive, especially in asymptomatic NMOSD patients. HyperCKemia in NMOSD has been reported in the setting of normal muscle histology (Di Filippo et al., 2012). Despite marked hyperCKemia, minimal muscle abnormality on light microscopy is seen (Malik et al., 2014). Sampling error on muscle biopsy may explain why some NMOSD patients with hyperCKemia have normal light microscopy findings on biopsy (Guo et al., 2014). Myocardial and diffuse skeletal muscle signal changes have also been described on MRI (Cosgrove et al., 2014; Deguchi et al., 2013). Interestingly, one of our patients was noted to have signal change in thoracic paraspinal muscles on MR imaging that was reported as "nonspecific signal abnormality in the midthoracic paraspinal musculature which may represent underlying myositis without obvious fluid collection to suggest abscess."

The role of antibody in pathophysiology also remains elusive. It is still not clear if such NMOSD myopathic patients have antibody and/or cell-mediated immune processes targeting AQP4 or other NMOSD-associated antigens on muscle (Deguchi et al., 2012; Okada et al., 2013; Suzuki et al., 2010; Yokoyama et al., 2012). Guo et al. demonstrated loss of immunoreactivity to myofiber surface AQP4 and the presence of complement-activating IgG antibodies directed at the sarcolemmal AQP4 (Guo et al., 2014). The role of antigens other than MOG is also not known. Whether muscle involvement represents an initial manifestation of NMOSD disease activity remains to be established.

Our study faced clear limitations for several reasons. It was a retrospective study of a rare condition. We assessed a lab value that is rarely checked in NMOSD. As shown by our data, patients often do not report myopathic symptoms. Thus, most of our patients had CK levels checked only as part of routine laboratory testing. While we could not standardize the timing of CK testing, we made certain to account for potential confounders as documented in patient records. Furthermore, while corroborative muscle MRI imaging and/or biopsy would have been ideal, both modalities do not always capture subtle muscle injury that would otherwise only be noted through CK elevation.

To reiterate, 4 out of our 43 tested NMOSD patients had no clearly defined etiologic basis or explanation for their hyperCKemia and muscle injury (i.e. statin use, thyroid disease, trauma, seizures, and toxins). This incidence is worth noting, as it is higher than would be expected from chance alone. A population study from Norway showed a prevalence of idiopathic hyperCKemia of only 0.71% in healthy adult controls (Brewster et al., 2007). A separate population-based Dutch study reported median normal CK values of 88 IU/L and 149 IU/L in white and black healthy adult controls, respectively, which is far lower than in our 4 patients (Lilleng et al., 2011). When taken together with prior studies showing an association between hyperCKemia and NMOSD, it must be asked whether hyperCKemia or subclinical myopathy falls under the spectrum of NMOSD. As previously noted, AQ4 is not limited to the CNS, but present in other tissue, including muscle.

5. Conclusions

In conclusion, we recommend that clinicians managing NMOSD patients screen for symptoms of subclinical myopathy or hyperCKemia, particularly during disease exacerbation. The role and clinical utility of serum CK as a screening tool in all NMOSD patients, however, remains to be further validated in larger prospective studies.

Declarations of interest

None.

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