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CASE REPORT

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Bulbospinal muscular atrophy (Kennedy disease) responsive to immunoglobulins?

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Abstract

A 61 year old man with facial diplegia, quadruparesis, tongue atrophy/fasciculations, bulbar speech, muscle weakness/wasting, hypotonia, tremor, dysdiadochokinesia, absent tendon reflexes, fasciculations, and gynecomastia, received immunoglobulins for suspected immune-neuropathy with limited benefit. After reconsideration, Kennedy disease was diagnosed upon 44 CAG repeats in *AR*. In conclusion, immunoglobulins exhibit limited benefit on immune-neuropathy in patients with coexisting KD.

KEYWORDS

immunoglobulins, Kennedy disease, motor neuron disease, phenotype, polyglutamine disease, polyneuropathy

1 | INTRODUCTION

Bulbar and spinal muscular atrophy (BSMA), also known as Kennedy disease (KD), is an X-linked condition due to expansion of a CAG repeat >38 in exon 1 of the androgen receptor (*AG*) gene (poly-glutamine disease).[1] Phenotypically, KD manifests as motor neuron disease with slowly progressive weakness and wasting of facial, limb, and bulbar muscles, while axial muscles are usually spared.[2] Here, we present a KD patient whose presentation suggested immune-neuropathy in addition to his genetic defect who seemingly profited from immunoglobulins.

2 | CASE REPORT

The patient is a 61 year old man, height 175 cm, weight 100 kg, with a 13-year history of hyper-CK (creatine-kinase) emia (Table 1) and a 10 year history of positional tremor, who developed weakness for abducting the right fifth finger 1 year prior to admission. Shortly afterward, he developed paresthesias of all fingers and toes bilaterally. Since about 6 m prior to admission, he experienced lumbago with radiation to the lower legs bilaterally with left-sided predominance. Two months prior to admission, he developed anginal chest pain. Cardiologic work-up only revealed arterial hypertension with mild thickening of the left ventricular myocardium. The stress test had to be discontinued at 80 W because of upcoming muscle weakness. Neurologic work-up then revealed weakness for head anteflexion, tongue atrophy, tongue fasciculations, bulbar speech, diffuse muscle weakness (M4), diffuse, mild wasting, muscle hypotonia, positional tremor, dysdiadochokinesia, and absent tendon reflexes on the upper limbs, bilateral gynecomastia, weakness for hip flexion (M4-), absent lower limb tendon reflexes, and fasciculations over the calves. Abdominal ultrasound revealed steatosis hepatis. X-ray respectively MRI of the lumbar spine revealed vertebrostenosis L4/5, osteochondrosis L3/4

and L5/S1, spondylarthrosis L2-5, and lumbar spondylosis. Proposed work-up for motor neuron disease and primary myopathy was not translated. The history was additionally positive for two syncopes, nicotine misuse, and frequent hookah consumption.

Two months later, the patient was admitted because of a fall due to weakness of the lower limbs. Neurologic examination revealed bilateral peripheral facial palsy, tongue atrophy, tongue fasciculations, quadruparesis (M3-4), stocking-type sensory disturbances, and broad-based, ataxic gait. Nerve conduction studies revealed sensorimotor polyneuropathy with conduction blocks over the median, ulnar, and left peroneal nerves, respectively (Table 2). Cerebral computed tomography was noninformative. CK was 1340 U/L (n, 20-200 U/L). HbA1c was 6.4% (n, 4%-6%). Folic acid was decreased to 3.68 ng/mL (n, 398-26.8 ng/mL) (Table 1). Thyroideastimulating hormone, vitamin-B12 levels, and immunofixation, antiganglioside antibodies, and Borrelia antibodies were normal. Cerebrospinal fluid investigations revealed 24/cells/μL but normal protein and glucose. Differential diagnoses considered were chronic inflammatory demyelinating polyneuropathy (CIDP), Lewis-Sumner syndrome (LSS), and multifocal motor neuropathy (MMN). Immunoglobulins were given resulting in partial remission of the conduction block in the median nerve and partial resolution of the gait disturbance but clinical examination remained otherwise unchanged to the pretreatment abnormalities. Because of long-term hyper-CKemia, bulbar manifestations, and gynecomastia, KD was additionally suspected. Genetic work-up confirmed the suspicion revealing 44 CAG triplets in the *AG* gene. The patient was released with amlodipine/valsartan, pantoprazole, metamizol, and gabapentin. Follow-up nerve conduction studies, 4 weeks after dismissal, confirmed the previous findings.

Key Clinical Message

A 61 year old man, with hyper-CKemia and positional tremor, developed weakness for right 5th-finger abduction 1 year earlier followed by paresthesias of all fingers/toes. Neurologic examination revealed quadruparesis, tongue atrophy/fasciculations, bulbar speech, muscle weakness and wasting, hypotonia, positional tremor, dysdiadochokinesia, absent tendon reflexes, fasciculations, and gynecomastia. Kennedy disease (KD) was suspected. Two months later, the patient presented with facial diplegia and worsening limb weakness. Since nerve conduction studies revealed multifocal conduction blocks, immune-neuropathy was suspected and immunoglobulins were given with limited effect. KD was diagnosed upon a 44 repeat CAG expansion in *AR*. Since deterioration suggests progression of KD, immunoglobulins should be avoided in KD.

3 | DISCUSSION

The presented patient is interesting for the rapid progression of KD, for the electrophysiological findings, and for the partial response to immunoglobulins. Particularly unusual in the presented patient are the multiple conduction blocks and the partial response to immunoglobulins. Whether the patient had both KD and an immune-neuropathy remains speculative but there are more arguments against the presence of an immune-neuropathy than in favor. Rapid progression of KD is not unusual,[3] why it is conceivable that affection of the facial muscles and worsening of limb muscle weakness rather reflects progression of the underlying genetic disease than CIDP/MMN/LSS with involvement of the facial muscles. Arguments against an immune-neuropathy are that there was no dissociation cyto-albuminique, that antiganglioside antibodies were all normal, that clinical improvement upon immunoglobulins was limited, that electrophysiological abnormalities (conduction blocks, axonal neuropathy) did not completely resolve upon immunoglobulins, and that the course was chronic progressive and not acute. Facial palsy is not unusual in KD, as it has been previously reported.[4] An argument in favor of an immune-neuropathy is that immune-neuropathy has been occasionally reported in ALS patients.[5]

Whether KD patients are more prone to acquire superimposed immune neuropathies than the general population remains speculative but it is conceivable that a damaged peripheral nerve is more vulnerable to infectious agents or immune attacks than an undamaged peripheral nerve. Immunoglobulins have not been reported as a treatment option for KD,[6] but KD has been occasionally misdiagnosed as immune-neuropathy, particularly POEMS syndrome.[7] Peculiarities of electrophysiological findings in KD have been previously reported.[8]

TABLE 1 Blood chemical values before an during hospitalization

Parameter	Reference limit	2/05	7/14	12/15	7/16	4/19	8/19
CK	38-174 U/L	934	nd	1232	941	1071	1201
GOT	0-50 U/L	51	38	40	33	nd	41
Thrombocytes	150-350 G/L	497	383	420	371	477	432
HbA1c	4%-6%	nd	nd	nd	nd	nd	6.5
Folic acid	3.89-26.8 ng/mL	nd	nd	nd	nd	nd	3.68

TABLE 2 Results of NCSs after rapid deterioration of the patient

	dL (ms)	NCV (m/s)	dSPA (mV)	pSPA (mV)
Before immunoglobulins				
Median nerve left	3.73	29.4	5.3	0.25
Median nerve right	4.42	51.0	5.0	5.0
Ulnar nerve left	4.17	51.5	1.49	1.26
Ulnar nerve right	3.0	47.6	3.4	2.2
Peroneal nerve left	4.06	36.3	0.78	0.39
Peroneal nerve right	3.99	39.0	1.23	1.02
After immunoglobulins				
Median nerve left	3.83	48.6	6.5	5.6
Median nerve right	4.68	51.2	4.1	3.6
Ulnar nerve right	3.38	53.3	3.0	2.1
Peroneal nerve left	4.77	36.8	1.43	0.62

Abbreviations: dL, distal latency; dSPA, distal amplitude; NCV, nerve conduction velocity; pSPA, proximal amplitude.

Subclinical or mildly manifesting involvement of the sensory nerves is not unusual in KD and has been also previously described.[9] Involvement of the sensory nerves has been confirmed by abnormal recordings of laser-evoked potentials.[10] If immune-neuropathy develops in a patient with KD, treatment with immunoglobulins should be carefully weighted with regard to a concrete benefit for the patient.

This case shows that KD may take a rapidly progressive course, and that it may go along with involvement of the facial muscles and the sensory system. KD may be accompanied by superimposed neuropathy with conduction blocks but immunoglobulins should be applied only if a true benefit for the second trouble can be expected. Immunoglobulins exhibit limited benefit on immune-mediated neuropathy in patients with coexisting KD.

CONFLICT OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

KP, S-PP, E-LP: data collection, literature search, critical comments. JF: first draft, data collection, evaluation of data.

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