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Anti-Kelch-like protein 11 (KLHL11) antibody associated encephalitis –Two case reports and review of the literature

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Abstract

Introduction

Kelch-like protein 11 antibodies (KLHL11-IgG) were first described in 2019 as a marker of paraneoplastic neurological syndromes (PNS). They have mostly been associated with testicular germ cell tumours (tGCT).

Methods

Report of two patients with KLHL11-IgG encephalitis and comprehensive review of literature.

Results

Patient 1 had been in remission from a tGCT 10 years prior. He developed episodic vertigo and diplopia progressing over a few days. Treatment with corticosteroids (CS) was started few days after symptom-onset.

Patient 2 had transient diplopia which resolved spontaneously. Visual problems persisted for 7 months, when he additionally developed a progressive cerebellar syndrome. 1 year after onset, CS treatment was started.

Initial MRIs were unremarkable in both patients, but analysis of cerebrospinal fluid (CSF) revealed chronic inflammation. KLHL11-IgG was positive in both patients (Patient 1 only in CSF, patient 2 in serum). Neoplastic screening has so far not revealed any signs of active underlying malignancy.

We found 15 publications of 112 patients in total with KLHL11-IgG encephalitis. Most patients (n=82) had a cerebellar syndrome with or without signs of rhombencephalitis. The most common symptoms were ataxia (n=82) and vertigo (n=47), followed by oculomotor disturbances (n=35) and hearing disorders (n=31). 80 of 84 patients had a GCT as an underlying tumour.

Conclusion

Our cases demonstrate classical symptoms of KLHL11-IgG encephalitis. An early diagnosis and therapy is imperative. As with other PNS, clinical awareness is needed and further studies are required especially in regard to therapeutic management.

Introduction

Antibodies targeting neuronal epitopes were first recognized in the early 1980s [1–3] in patients with paraneoplastic neurological syndromes (PNS). These neural autoantibodies are divided into autoantibodies against neuronal cell-surface antigens (neuronal surface antibodies, NSA) and autoantibodies against intracellular neuronal antigens. The latter are often associated with malignant tumours[4] and in these cases are denominated as onconeural antibodies (onconeural-abs) due to the expression of the neuronal antigen in the tumour. Because of their intracellular localisation, the main pathogenic mechanism is believed to be T-cell-mediated[5]. There are commercially available tests to search for classical onconeural-abs (e.g. Yo, Hu, Ri, Ma1/2, Amphiphysin, CV2, SOX1)[6]. Current diagnostic criteria include more recently discovered autoantibodies[7], among these Kelch-like protein 11 antibodies (KLHL11-IgG), which were first described in 2019[8,9]. Detection of KLHL11-IgG in serum and/or cerebrospinal fluid (CSF) combined with a clinical syndrome compatible with autoimmune encephalitis should lead to cancer screening[10]. In addition to a recent review[13], we present two new cases recently diagnosed at our University Hospital in Bern and perform a comprehensive review of all the published cases.

Methods

Case reports

Cases were summarized based on the available clinical and paraclinical findings (MRI, CSF, serum analyses) of both patients until 01-Sept 2022.

Literature research

The literature search was conducted using Pubmed, last search on 30.09.2022. We found 11 publications reporting cases associated with KLHL11-IgG under the keywords "KLHL11 antibody" OR "KLHL11 antibodies" OR "KLHL11 autoimmunity"[9,11–20].

All the other literature was found by the references of the aforementioned papers.

Ethics statement

We obtained written informed consent by the two patients presented here prior to publication.

Case presentation

Case 1

A 47-year-old man developed acute episodic vertigo with vertical diplopia. He presented in a primary care hospital the next day where a stroke was postulated, but not confirmed by cerebral magnetic resonance imaging (cMRI). Clinical examination was documented as unrevealing. Symptoms progressed steadily with consecutive consultation of an ophthalmologist and transfer to our neurological department 2 weeks after onset.

On physical examination, there was a spontaneous torsional down-beat nystagmus, skew deviation with hypertropia of the right eye and mild gait ataxia. He had no cognitive deficits, hypoacusis, headaches, constitutional symptoms or signs of infection. Medical history revealed a testicular mixed germ cell tumour (tGCT) 10 years earlier, which had been curatively treated with unilateral orchiectomy and chemotherapy without any signs of relapse in the follow-up. He smoked occasionally and reported moderate alcohol consumption (3-4 glasses of wine per week). cMRI (incl. 3mm imaging of brainstem) showed no abnormalities. CSF-analysis revealed mild mononuclear pleocytosis (16 cells/ul), elevated protein levels (0.51 g/l) and CSF-specific oligoclonal bands (OCBs type II). There was no evidence of infectious causes. Classical onconeural-abs as well as NSA were negative in serum and CSF (detailed results in supplement table 1-3). Seronegative autoimmune encephalitis was presumed and 3 weeks after onset a corticosteroid (CS) therapy was started (intravenous methylprednisolone 1 g/d for cumulatively 6 days followed by oral prednisolone 1 mg/kg bodyweight with slow tapering). Symptoms improved partially (persisting subjective unsteadiness) and stabilized. Cell-based indirect immunofluorescence assay (CBA) for KLHL11-IgG was performed and found positive in CSF (1:1000) and negative in serum 1:100 diluted.

Three months after onset, he developed symptoms of a neuralgic shoulder amyotrophy, which resolved after a few weeks. Etiology remained unclear (details in Supplementary). A possible peripheral KLHL11-IgG manifestation can be hypothesized, which so far has not been described in the literature.

So far, neoplastic screening, incl. thoracoabdominal-CT-scan (t/aCT) and positron-emission-tomography (PET-scan), has not revealed any signs of a tumour or recurrence of the tGCT. Testicular sonography and urological examination showed no signs of malignancy (e.g. fibrosis, testicular atrophy or microlithiasis)[21,22]. After 26 weeks of CS-treatment a steroid-sparing therapy with azathioprine (1,5 mg/kg bodyweight) was started and tumour screenings are planned in regular intervals. At the last follow-up (8 months after symptom-onset) he continued having difficulties focussing objects. A down-beat torsional nystagmus in the lateral gaze persists, without any other focal neurological deficits. Follow-up cMRI has remained normal.

Case 2

This 43-year-old man suffered an episode of diplopia, which started subacutely over a period of a few days and resolved spontaneously within 2 weeks. Because of mild persistent visual problems with fast moving objects (e.g. tracking the ball when playing tennis) he presented at our ophthalmology outpatient clinic. Examination and medical history were unremarkable; he

was a smoker (cumulative 12 pack years) and reported moderate alcohol consumption. The episode was interpreted as a possible transient trochlear palsy and no further investigations were undertaken.

Approximately 6 months afterwards he developed progressive gait problems. A neurologist in private practice could not objectify the symptoms. Brain and spine MRI were normal. Within 2 months symptoms progressed and he required bilateral crutches for walking. A functional neurological gait disorder was suspected because of the un-ergonomic wide-based gait. However, the patient showed an up-beat nystagmus and a reduced coordination of the left arm and diagnostic work-up showed CSF-specific OCBs type II (normal cell count, slight elevated protein level of 0.5 g/l). Classical onconeural-abs, electrophysiological examinations (sensory and motor evoked potentials) and neoplasia screening with t/aCT remained unremarkable. He was transferred to our neuroimmunological outpatient clinic for further evaluation.

On presentation, the patient had dysarthria with slurred speech, macro square wave-jerks, a spontaneous up-beat nystagmus and distorted suppression of the vestibulo-ocular reflex. He had appendicular ataxia (more pronounced on the left side), titubations as well as a wide-based ataxic gait and was unable to stand without assistance. The maximal walking distance with crutches was 150 m, with multiple recent falls. Sensory as well as motor functions were otherwise normal. SARA-Score (Scale for the Assessment and Rating of Ataxia) was 16/40 points. Seven weeks later, symptoms had progressed further with need of a wheelchair and maximal walking distance (rolling walker) of a few meters (SARA-Score 25/40 points). Follow-up cMRI remained unremarkable, whereas CSF now showed a mild mononuclear pleocytosis (11 cells/ul), while other CSF parameters remained unchanged. Classical onconeural-abs as well as NSA were negative in serum and CSF (detailed results in supplement table 1-3). A neoplasia screening (t/aCT, PET-scan, testicular sonography, colonoscopy and gastroduodenoscopy) revealed no signs of an active tumour. A primary autoimmune cerebellar ataxia was suspected and 15 months after onset CS-treatment was started (intravenous methylprednisolone 1g/d i.v. for 5 days, followed by oral prednisolone 1 mg/kg bodyweight). He was transferred to a rehabilitation clinic. He improved clinically (SARA-Score 18/40), but follow-up cMRI (20 months after onset) revealed cerebellar atrophy. Serum KLHL11-IgG was analysed (no CSF available) and found positive (1:160.000). After 8 months of high-dose oral CS-therapy (prednisolone 70 mg/d), a second line therapy with Rituximab was initiated. Clinically, he further improved (SARA-Score 16/40 points). CS-therapy was slowly tapered to one fourth of the initial dose, but symptoms progressed again (SARA-Score 20/40 points), leading to an add-on therapy with Azathioprine (target-dose 2,5 mg/kg bodyweight), which was not well tolerated. Thus the second-line therapy was changed to cyclophosphamide (15mg/kg bodyweight for 6 cycles). At the last follow-up (28 months after symptom-onset) the maximal walking distance (walker) was 30 metres with otherwise need of a wheelchair. The SARA-Score remained stable (18/40 points).

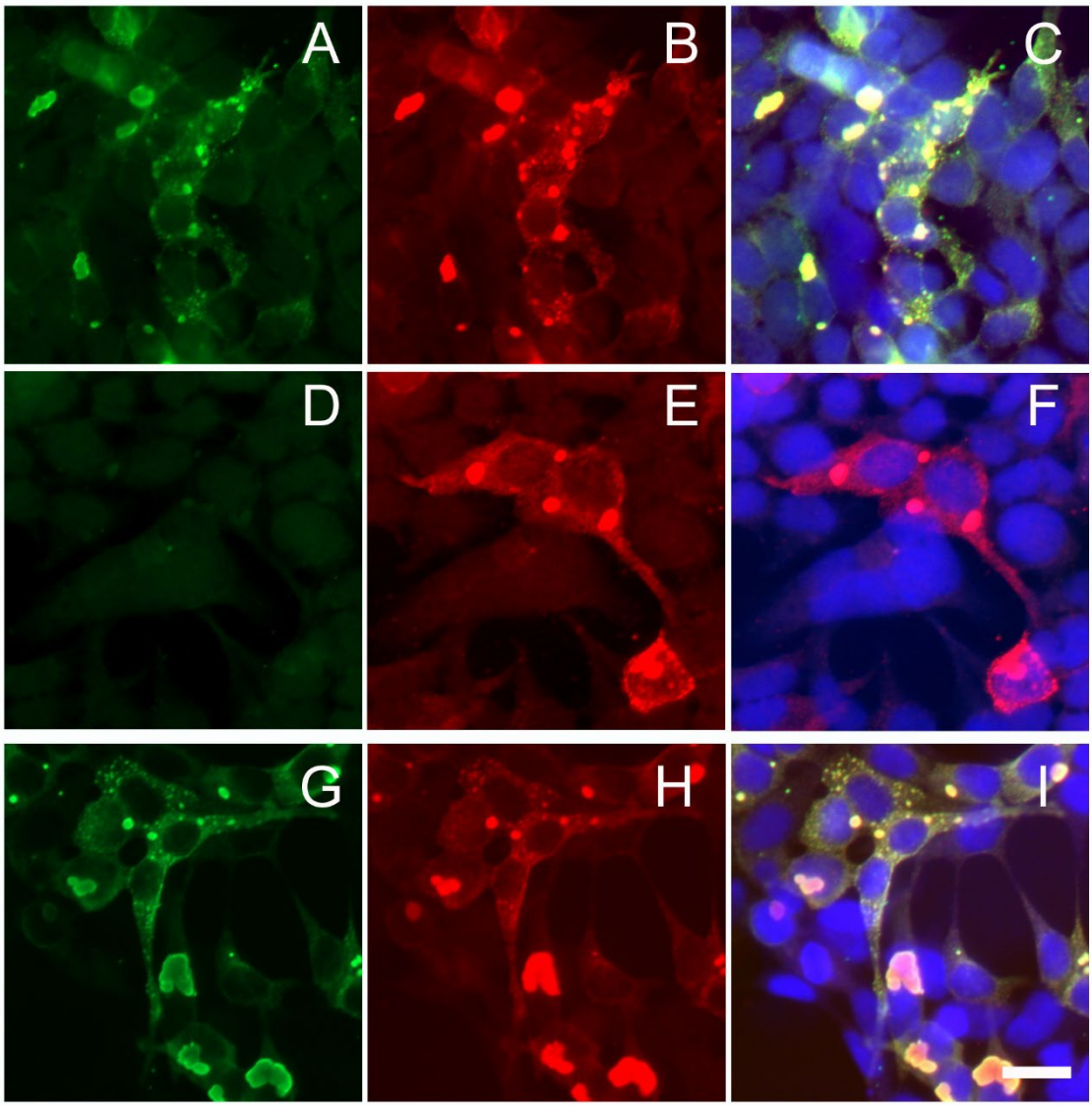

Figure 1: Cell based assay with indirect immunofluorescence of the presented cases. In case 1 (A-F), only cerebrospinal fluid (CSF) was positive (A, dilution 1/1000), while serum was negative (D, dilution 1/100). In case 2 (G-I), only testing of serum was possible, which was positive (G, dilution 1/10.000). For this assay, Kelch-like protein 11 (KLHL11) transfected HEK cells were used. Green = patient material. Red = standardized commercially available antibody against KLHL11. Blue = nuclear staining. Test is considered positive, if there is an overlap of the fluorescence corresponding to the patient sample with the one corresponding to the commercially available antibody.

Literature review

The first 13 patients with KLHL11-IgG associated encephalitis were published in 2019[9]. The index patient of this case series had developed progressive vertigo, truncal and appendicular ataxia almost 4 years after diagnosis and therapy of a testicular seminoma[9].

So far, 112 patients with KLHL11-IgG associated encephalitis have been reported in the literature (table 1)[9,11–20,23–28].

Demographic characteristics

Most patients were men (n=95) and middle aged (around 65% aged 30-59 years), while 23% of patients were young adults (<30 years of age). Most female patients (16/17) were reported in one case series, where KLHL11-IgG were retrospectively analysed in patients with different neurological syndromes[12].

Clinical syndrome/symptoms

The most common symptom-complex was a cerebellar syndrome and/or a rhombencephalitis (82/112 patients, fig. 2), mostly as part of a multi-system neurological disorder. Only in 12 patients, an isolated cerebellar syndrome was reported. In 20/112 patients, a limbic encephalitis was reported, 11 patients of these had additional signs of rhombencephalitis. 6/112 had an opsoclonus-myoclonus syndrome, all of which were female[12,17]. 5/112 patients had a cerebellar syndrome with spinal cord manifestation, mostly (n=4) described as long extensive spinal cord lesions[13,14,19]. In some patients, symptom-onset has been reported as sudden or even episodic, but in the long term without therapy, symptoms progress to a complete (cerebellar) syndrome in most patients[19]. In 78/112 patients time from onset to neurological deficits was reported and the time span in those cases was 2 months up to 2 years[13,14,19,28,29]. Nevertheless, the exact disease course of some of the published cases is unclear; therefore, a more detailed description of disease progression (e.g. time to loss of ambulation) is not possible at present.

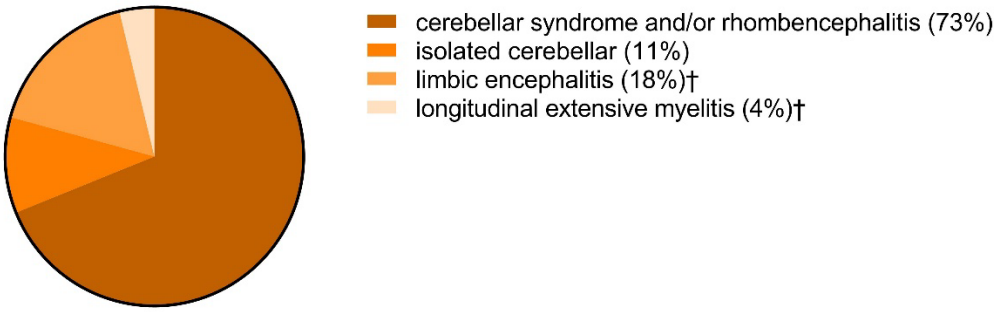

Figure 2: clinical syndrome of KLHL11-IgG in percentage of all patients reported.
† Can be present with or without a cerebellar syndrome.

The most common documented symptoms were ataxia (82/112 patients, appendicular, gait or truncal; fig. 3) and vertigo (47/112 patients). Other common symptoms were hearing disorders (31/112 patients), oculomotor disturbances (35/112 patients) and behavioural/cognitive symptoms (26/112 patients). Some patients also experienced dysarthria (9/112 patients) and/or seizures (10/112 patients).

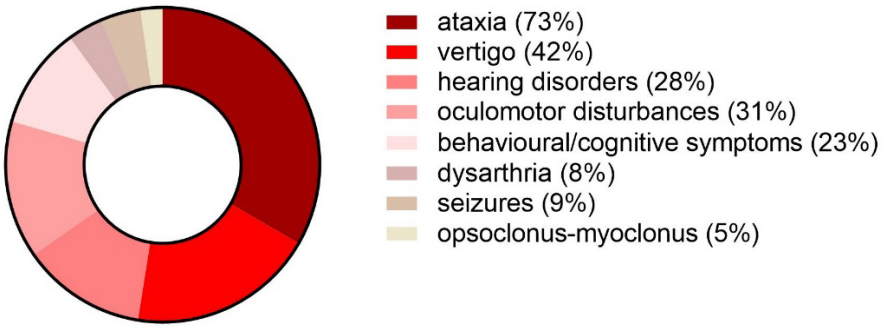

Figure 3: symptoms or signs reported by patients with KLHL11-IgG encephalitis in percentage of all patients reported.

Imaging and paraclinical findings

Imaging features were reported in 80/112 patients. Most of them (n=55) had pathologic imaging findings (at time of diagnosis or on follow-up). One common finding was cerebellar atrophy (n=27). Another common finding was hypertrophic olivary degeneration (n=6). In 2 patients a "hot cross bun" sign was described[18,20,30]. T2/FLAIR-hyperintensities have been described in different regions of the brain, but most commonly in brainstem, cerebellum or hippocampi/temporal lobe. A few patients had spinal cord lesions, either short segmented or long extensive.

CSF-analysis revealed an inflammatory profile in almost all patients with reported CSF findings (64/73 patients, in the remaining 39 patients no CSF-analysis was reported). A common finding (n=57) were (CSF-specific) oligoclonal bands. Concurrent detection of other onconeural-abs (e.g. Ma2, Hu) or NSA, like N-Methyl-D-Aspartate receptor (NMDAR) autoantibodies (ab), was reported in 23/112 patients: Ma2-ab (7/112 patients), antibodies against leucine zipper 4 (LUZP4-ab, 8/112 patients), Hu-ab (1/112 patient) and NMDAR-ab (7/112 patients). The latter patients had a classical NMDAR-encephalitis and detection of KLHL11-IgG did not appear to have clinical implications[31].

Associated tumours

A tumour was reported in 84/112 patients. Most (n=80) had a GCT (incl. seminomas and/or teratomas), either of gonadal or extragonadal origin (e.g. thymic GCT)[12]. In 57/112 cases, the tumour was newly diagnosed after screening, whereas in 5/112 cases a tumour was already known (either active or considered in remission). In one case, the tumour was diagnosed 13 years prior and a relapse was found during tumour screening after KLHL11-IgG detection[19]. In the rest of the patients (24/112 patients), the time point of the diagnosis of the tumour was not clearly stated. In 2/112 patients testicular hypoechoic lesions, fibrosis or microlithiasis was described on ultrasound, a finding which is considered suspicious of a regressed testicular tumour[21,22]. In 17 patients a regressed ("burned-out") tGCT was only found on histological examination (after orchiectomy).

Treatment approaches

An immunotherapeutical approach was addressed in 79/112 patients. All 79 patients received a first-line immunotherapy: 65 intravenous methylprednisolone (IVMP) followed by oral CS-therapy in 17 (duration not clearly reported); 33 patients intravenous immunoglobulins (IVIG) and 27 patients plasma exchange (PLEX). 51 patients received a second-line immunotherapy: 33 cyclophosphamide (CPA), 22 rituximab (RTX), 1 natalizumab (NTZ), 3 mycophenolate mofetil (MMF), 1 azathioprine (AZA) and 1 tacrolimus (TAC).

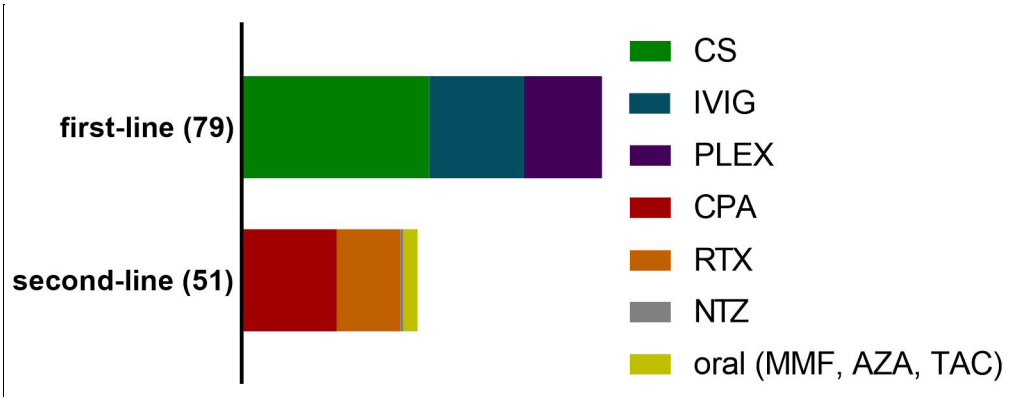

Figure 4: immunotherapeutical approach. CS = corticosteroids (intravenous and/or oral). IVIG = intravenous immunoglobulins. PLEX = plasma exchange. CPA = cyclophosphamide. RTX = rituximab. NTZ = natalizumab. MMF = mycophenolate mofetil. AZA = azathioprine. TAC = tacrolimus.

Outcome

The disease course under immunotherapy was reported in all 79 treated patients (fig. 5): 34 patients further deteriorated, 29 patients remained stable and 16 improved. For patients receiving a first-line immunotherapy (38 patients), disease course was clearly reported in 16 patients: 8 remained stable (follow-up 2-216 months), 7 deteriorated further (follow-up 2-133 months) and only 1 improved (follow-up 37 months). For patients receiving a second-line immunotherapy (50 patients), disease course was clearly reported in 31 patients: 21 deteriorated, 8 patients remained stable and 5 improved.

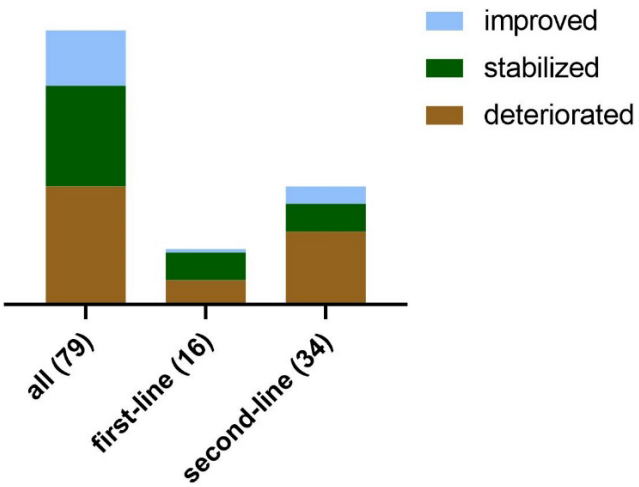

Figure 5: clinical disease course after immunotherapy. Disease course was reported for 79 patients and in detail only for 50 patients, of which 16 received only a first-line therapy.

Deambulation or disability as scored by the modified Rankin scale (mRS) was reported in 38 patients (fig. 6), while in a case series of 39 patients, a median of 4 (range 2-6) was reported[13]. Of the 38 patients, 16 had severe deficits or were at least wheelchair-bound (mRS 4-5), 7 patients needed assistance for walking (mRS 3) and 6 patients had an mRS < 3. Of the above mentioned 79 patients, 16 were reported as dead at the time point of the respective publication. Cognitive outcomes have so far not been fully addressed and are not reflected on the mRS.

Figure 6: clinical disease course as scored by the modified Rankin Scale (mRS): 16% no relevant disability (mRS 1-2), 18% moderate disability (mRS 3), 42% severe disability and/or loss of ambulation (mRS 4-5). 24% died (mRS 6).

Cohort [Ref.]	Patient number	Sex	Age (median)	Symptoms	Imaging	KLHL11-Antibody-titer (range)	CSF§	Tumour
1[9]†	1	m	65	vertigo, ataxia, diplopia, SNHL	pathologic (11/13) †: 6/13 cerebellar atrophy, 2/13 T2/FLAIR-hyperintensity (1/13 midbrain, 1/13 cerebellar nuclei), 1/13 LME, 1/13 HOD, 2/13 bilateral mesial temporal-lobe abnormalities	serum-median 1:15,360 (1:960-1:244,800) CSF-median 1:712	C+/P+/OCB	testicular seminoma
	2	m	51	vertigo, ataxia, diplopia, SNHL			C+/P+/OCB	testicular seminoma
	3	m	45	diplopia, ataxia, seizures			C+/P+	none (testicular fibrosis, microlithiasis)
	4	m	28	vertigo, ataxia, diplopia, SNHL			C+/P+	testicular seminoma
	5	m	43	vertigo, ataxia, SNHL			P+/OCB	extratesticular seminoma
	6	m	36	visuospatial disorientation, memory loss, suicidal ideation, SNHL, trigeminal neuropathy			C+/P+/OCB	testicular seminoma
	7	m	29	vertigo, ataxia, diplopia, SNHL			C+/P+/OCB	extratesticular seminoma
	8	m	42	dysarthria, ataxia			P+	none (testicular fibrosis, microlithiasis)
	9	m	68	vertigo, ataxia, SNHL			P+/OCB	testicular seminoma
	10	m	41	dysarthria, ataxia, headaches			C+/P+	extratesticular seminoma
	11	m	37	vertigo, diplopia, ataxia			C+/P+/OCB	testicular seminoma
	12	m	40	vertigo, diplopia, ataxia			C+/P+/OCB	testicular seminoma
	13	m	27	dysarthria, left upper-extremity tremor, imbalance			OCB	testicular seminoma

2[11]	14	m	32	vertigo, ataxia, diplopia, SNHL	hippocampal and cerebellar T2/FLAIR-hyperintensity	n/r	P+/OCB	n/r
3[12]	15-21	m:f 5:2	15-57 (43)	cerebellar ataxia	n/r	serum-median 1:10.000 CSF-median (13/22) 1:1000	n/r	2 seminoma, 2 ovarian teratoma, 2 testicular teratoma, 1 thymic germ cell tumour
	22-27	m	22-65 (37)	brainstem diencephalic encephalitis	n/r		n/r	2 seminoma, 2 tGCT, 1 small cell lung cancer
	28-32	f	31-48 (37)	opsoclonus myoclonus	n/r		n/r	ovarian carcinoma (1/5) and ovarian teratoma (1/5)
	33-35	m:f 2:1	12-76 (48)	LE	n/r		n/r	testicular teratoma (1/3)
	36-37	m:f 1:1	f: 26 m: 19	chronic psychosis	n/r		n/r	teratoma (2/2)
	38	f	36	subacute encephalitis	n/r		n/r	ovarian teratoma
	39	m	9	extralimbic encephalitis	n/r		n/r	none found
	40-46	m:f 1:6	13-29 (19)	no symptom reported. 7/7: NMDAR-antibodies associated encephalitis.	n/r		n/r	ovarian teratoma (5/7)

4[13]	47-72†	m	28-73 (46)	symptoms: ataxia (21p), diplopia (15p), vertigo (13p), SNHL (8p); seizures (8p) syndromes: RBE (15p), LE (6p), combined RBE+LE (5p)	pathologic (30/37) at baseline†: - 28/37 T2/FLAIR-hyperintensities (12/28 temporal lobe, 9/28 cerebellar, 3/28 brainstem, 3/28 diencephalon, 1/28 long extending lesion in central grey structures from mesencephalon to thoracic SC); - 5/37 contrast-enhancement (2/5 temporal lobe, 1/5 midbrain+spinal roots, 1/5 isolated in trigeminal nerve, 1/5 LME) F/u (12/37): 6/12 cerebellar atrophy, 2/12 medial temporal lobe atrophy, 1/12 diffuse cerebral atrophy, 3/12 HOD	serum-median†: 1:30,720 (1:960-1:245,760) CSF†: >1:640	Available in 34/39: 29p inflammatory liquor (C+/P+), 18/22p OCB	25/36 (3p not screened): testicular tumour (23), pulmonary adenocarcinoma (1), chronic lymphatic leukaemia (1)
5[14]††	73	m	(<30y)	RBE (initially: vertigo)	normal	serum-median 1:15,360 (1:50-1:245,760)	C+/P+/OCB	seminoma
	74	m	(30-59y)	acute vertigo, SNHL, tinnitus	cerebellar atrophy		C+/P+/OCB	seminoma
	75	m	(30-59y)	RBE (initially: acute vertigo)	cerebellar atrophy, cerebral T2/FLAIR-hyperintensities		C+/P+/OCB	"burned-out" tGCT
	76	m	(30-59y)	RBE (initially: ataxia, diplopia, tinnitus, weakness, tremor)	normal		C+/P+/OCB	seminoma
	77	m	(30-59y)	RBE (initially: SNHL)	cerebellar atrophy		C+/P+/OCB	"burned-out" tGCT
	78	m	(>60y)	RBE (initially: ataxia, diplopia, tinnitus)	cerebellar atrophy		C+/P+/OCB	seminoma
	79	m	(30-59y)	RBE (initially: acute vertigo)	normal		C+/P+/OCB	"burned-out" tGCT
	80	m	(<30y)	RBE (initially: SNHL, tinnitus)	cerebellar atrophy, bilateral IAC-enhancement		C+/P+/OCB	extratesticular seminoma
	81	m	(30-59y)	RBE (initially: ataxia, weakness)	cerebellar T2-hyperintensities		C+/P+	seminoma
	82	m	(30-59y)	RBE (initially: SNHL, tinnitus)	cerebellar atrophy, cerebral T2/FLAIR-hyperintensities		P+/OCB	extratesticular seminoma

	83	m	(30-59y)	RBE (initially: acute vertigo, SNHL)	bilateral IAC, enhancement, HOD	CSF-median 1:640 (1:256-1:640)	C+/P+/OCB	seminoma
	84	m	(30-59y)	RBE (initially: acute vertigo, dysarthria, lower limb weakness)	cerebellar atrophy, pontine T2/FLAIR-hyperintensities, cerebellar LME		C+/P+/OCB	extratesticular seminoma
	85	m	(>60y)	RBE (initially: acute vertigo)	cerebellar atrophy		P+/OCB	mixed testicular cancer
	86	m	(30-59y)	RBE (initially: acute vertigo)	IAC enhancement		C+/P+	“burned-out” tGCT
	87	m	(30-59y)	n/r (initial history unknown)	brainstem atrophy		C+	seminoma
	88	m	(30-59y)	RBE (initially: acute vertigo)	T2/FLAIR-hyperintensities in cervical SC, brainstem, thalamus		C+/P+/OCB	none
	89	m	(30-59y)	RBE (initially: acute vertigo)	brainstem T2/FLAIR-hyperintensities		P+	“burned-out” tGCT
	90	m	(>60y)	RBE (initially: diplopia, weakness in lower limb)	cerebellar atrophy		P+/OCB	lung adenocarcinoma
	91	m	(30-59y)	RBE (initially: ataxia, visual difficulties, acute vertigo)	cerebellar atrophy		P+	seminoma
	92	m	(30-59y)	RBE (initially: SNHL)	cerebellar atrophy, HOD, T2/FLAIR-hyperintensities in brainstem, cerebellum, thalamus		C+/P+/OCB	“burned-out” tGCT
6[15]	93	m	45	vertigo, diplopia, dysarthria, sleep-related central hypoventilation syndrome (ondine’s syndrome), trismus, sensory deficits facial	pontine T2/FLAIR-hyperintensity	serum: 1:3840 CSF: 1:64	OCB	“burned-out” tGCT
7[16]	94	m	45	ataxia, SNHL, vertigo, dysarthria	normal	n/r	C+/P+	recurring seminoma
8[17]	95	f	37	vertigo, opsoclonus-myoclonus (opsoclonus, arrhythmic action tremor, dysarthria, ataxia, tremor)	normal	n/r	C+/P+/OCB	none
9[18,32]	96	m	42	progressive ataxia, SHNL	brainstem/cerebellar atrophy, “hot cross-bun” sign	n/r	C+/P+/OCB	metastasized “burned-out” tGCT
10[27]	97	m	58	vertigo, oscillopsia, ataxia	cerebellar T2/FLAIR-hyperintensities	n/r	“inflammatory” (not defined)	Seminoma
11[19]	98	m	47	sudden onset: ataxia, vertigo; also cognitive symptoms/dysexecutive syndrome	cerebellar T2/FLAIR-hyperintensity. F/u: cerebellar atrophy	n/r	C+/P+/OCB	“burned-out” tGCT

	99	m	46	subacute onset: ataxia, dysarthria; also hypersomnia, ophthalmoplegia, SNHL, paraparesis	contrast-enhancing brainstem lesion, F/u: cerebellar atrophy, myelitis	n/r	C+/P+/OCB	tGCT
	100	m	42	episodic ataxia, vertigo, dysarthria	cerebellar atrophy	n/r	C+/P+/OCB	"burned-out" tGCT
	101	m	43	episodic/paroxysmal: vertigo, ataxia; also dysexecutive syndrome	normal; F/u: cerebellar atrophy	n/r	C+/P+/OCB	"burned-out" tGCT
	102	m	35	sudden onset: vertigo, oscillopsia; also dysexecutive syndrome, seizures	T2/FLAIR-hyperintensity mesencephalon; contrast-enhancing lesion mesial temporal lobe and pons	n/r	C+/P+	mixed testicular cancer
	103	m	44	diplopia, ataxia, spasticity, memory deficits (limbic encephalitis)	hippocampal T2/FLAIR-hyperintensity and contralateral atrophy; F/u: cerebellar atrophy	n/r	P+/OCB	"burned-out" tGCT
	104	m	64	ataxia, dysarthria, tetrapyramidal syndrome, cognitive deficits	normal; F/u: cerebellar atrophy	n/r	C+/P+/OCB	none
	105	m	41	ataxia, vertigo, SNHL, dysarthria	T2/FLAIR-hyperintensity vermis, bi-hippocampal (one side with contrast-enhancement); F/u: hippocampal and cerebellar atrophy	n/r	P+	"burned-out" tGCT
	106	m	79	apathy, hypersomnia, ataxia, tremor, cognitive deficits (limbic encephalitis)	T2/FLAIR-hyperintensity both mesiotemporal lobes, unilateral hippocampal atrophy	n/r	C+/P+/OCB	none
	107	m	42	vertigo, ataxia, bilateral weakness, fasciculations, flail arm syndrome	LESCL (tract-specific, anterior cord); F/u: cerebellar and spinal cord atrophy	n/r	C+/P+/OCB	"burned-out" tGCT
	108	m	55	ataxia, dysarthria	normal	n/r	C+/P+	"burned-out" tGCT
12[20]	109	m	36	ataxia, diplopia, hearing loss	"hot cross-bun" sign	n/r	n/r	"burned-out" seminoma
13[25,26]	110	m	33	ataxia, tremor, dysarthria, vertigo	cerebellar atrophy	n/r	OCB	seminoma
14[23,24]	111	m	52	hearing loss, vertigo, followed by diplopia, ataxia; seizure	bi-thalamic T2-FLAIR-hyperintensities, later on: in brainstem, temporal and frontal lobe, as well as LESCL	serum 1:80,000, CSF 1:8,000	C+/P+/OCB	metastasized "burned-out" tGCT
15[28]	112	m	68	vertigo, visual disorders, ataxia; over time cognitive disorders	mild contrast-enhancement brainstem; F/u: global atrophy	serum 1:160,000 CSF 1:16,000	P+/OCB	"burned-out" tGCT
Our cases	113	m	47	diplopia (spontaneous, episodic), vertigo	normal	serum negative, CSF 1:1,000	C+/P+/OCB	tGCT clinically in complete resolution

	114	m	43	ataxia, vertigo, dysarthria, diplopia	cerebellar atrophy	serum 1:160,000	P+/OCB	none

Table 1: characteristics of the reported cases of patients with KLHL11-antibody associated encephalitis. Order according to date of publication.
† Dubey et al.(cohort 4)[13] pooled the results from the first 13 reported cases (cohort 1)[9] with 26 additional cases for analysis. †† ages reported as young (<30y), middle (30-59y) aged or older adult (>60y). § Oligoclonal bands (OCBs) only considered relevant if explicitly mentioned as pathologic, CSF-specific or number of reported CSF-specific bands ≥ 1.
Abbreviations: C+ = pleocytosis; CSF: cerebrospinal fluid; f = female; FLAIR = fluid attenuated inversion recovery; F/u = follow up; GCT = germ cell tumour; HOD = hypertrophic olivary degeneration; LE = limbic encephalitis; LESCL = long extensive spinal cord lesion; LME = leptomeningeal enhancement; m = male; n/r = not reported; OCB = oligoclonal bands; P+ = protein elevation; RBE = rhombencephalitis; SC = spinal cord; SNHL = sensorineural hearing loss; tGCT = testicular GCT

Discussion

Our two cases represent typical examples of patients with KLHL11-IgG encephalitis as well as the difficulties in diagnosing and managing this emerging disease. The clinical presentation of KLHL11-IgG encephalitis varies, but the most common clinical presentation is a cerebellar syndrome with signs of brainstem involvement (which is then defined as a rhombencephalitis). The most common symptoms are ataxia, vertigo, diplopia or oculomotor disorders, as well as sensorineural hearing loss. The latter has been associated both with a possible affection of the cochlear nucleus and of the spiral ganglion[14].

Symptoms can begin acutely, which might lead to the misdiagnosis of ischemic stroke, as was the case with our first patient. Around 9% of reported patients presented with seizures and around 18% (20/112) presented with symptoms of limbic encephalitis independent of concurrent autoantibodies (e.g. anti-NMDAR-abs)[9,13]. Also rare neurologic syndromes associated with brainstem involvement, such as sleep disorders (e.g. hypersomnia) [19,33], sleep-related central hypoventilation syndrome (Ondine's syndrome)[15] or trigeminal neuropathy[12] have been reported. Imaging is usually pathologic (around 69% of MRIs), whereby in a few patients an atrophy (especially cerebellar) is seen on follow-up. Uncommon findings like spinal cord manifestation might lead to misdiagnosis of other neuroimmunological disorders. Also brainstem and/or cerebellar T2-/FLAIR-hyperintensities and CSF-specific OCBs might prompt to the interpretation of a multiple sclerosis, hence the need for contextualization of the findings with the clinical presentation of the patient[13].

Prevalence of cases with KLHL11-IgG was estimated as per population-based epidemiology, using the Rochester Epidemiology Project database of Olmsted County (Minnesota, United States), at 1.4 cases per 100,000 people, and higher among men (2.79 cases per 100,000)[9]. This points to a probably higher prevalence of KLHL11-IgG than other classical onconeural-abs, for example the prevalence of Ri-autoantibodies is estimated at 0.6 cases per 100,000 people[34]. Analysis for KLHL11-IgG can be performed in a few laboratories worldwide. This together with the relative rarity of this new diagnosis can lead to a substantial delay in starting an immunotherapy and is probably one of the reasons for many missed diagnoses of this disease. To help decide which patients are more probable to have KLHL11-IgG associated encephalitis, Vogrig et al developed a clinical score (MATCH-score: male 1 point, ataxia or other cerebellar symptoms 1 point, testicular cancer or pre-malignancy such as microlithiasis/testicular fibrosis 2 point, cancer of other type 1 point, hearing alterations 1 point) with a cut-off ≥4 points suspicious for KLHL11-IgG associated encephalitis (sensitivity 78%, specificity 99%)[19]. Unfortunately, sensitivity of this score is relatively low, and if applied to all reported patients, it decreases to around 66% (74/114 patients). We therefore suggest evaluating a testing for KLHL11-IgG in any patient (independent of age) with acute or subacute ataxia (or by extension cerebellar symptoms with oculomotor disturbances, vertigo or hearing problems), if other differentials have been ruled out. This holds especially true in the context of history of GCT and inflammatory CSF findings, hinting towards a possible immunological aetiology.

The start of immunotherapy should not be delayed and started as soon as an immunological/paraneoplastic syndrome is suspected and an infectious cause has been ruled out. If a tumour is not known, a tumour screening (with especial emphasis on the gonads) is recommended,

since early detection and treatment (surgery and/or chemotherapy/radiotherapy) harbours not only therapeutic but also prognostic relevance for the patients[13]. As with other high-risk antibodies, if negative, screening is recommended to be repeated every 4-6 months for 2 years with a high sensitivity and specificity for PET-scan[7,35,36]. Testicular ultrasound should also be considered as findings like microlithiasis hints at a higher risk for a GCT[37,38]. Ultimately a "burned-out" GCT can only be diagnosed histologically, making the diagnosis challenging[21]. Tumour markers have limited utility[39,40]. For patients with a GCT in remission over a long period of time (months-years) an immune reaction independent of the initial trigger has been speculated[26], but so far there is not enough evidence to support this theory. On the contrary, in such patients KLHL11-IgG associated encephalitis should be considered as suspicious of a tumour relapse[41].

For PNS-diagnosis onconeural-abs-testing should be done both in serum and CSF[7]. Detection in serum alone (CSF negative) without appropriate clinical/CSF-findings can lead to misdiagnosis of PNS[42]. A combination of both immunohistochemistry (IHC)/immunofluorescence (IFA) and immunoblot or CBA is considered gold standard to optimize clinical specificity[7]. In most reported cases detection both in CSF and serum was reported. Use of both methods was reported in 85/112 patients, of which 59 were positive for both methods. In one of our patients (case 2) KLHL11-IgG was analysed and detected in serum, but not analysed in CSF. Since clinical and paraclinical constellation was considered compatible to KLHL11-IgG encephalitis we abstained from repeating a lumbar puncture to perform the analysis. Both techniques (CBA, IFA/IHC) were performed in our patient samples. IFA was negative in both, which could be related to methodological reasons (e.g. in case 1, IFA was initially sparsely positive and described as suspicious of positivity against neurofilament). A characteristic IFA-pattern ("sparkles pattern") in different brain regions (among them brainstem and hippocampus) has been described, but has been reported to be difficult to interpret without sufficient expertise with KLHL11-IgG[9,13]. As no tumour tissue was available (tGCT-diagnosis 10 years prior in case 1), we could not analyse for KLHL11-expression.

In general, management of KLHL11-IgG encephalitis is complicated by the treatment-refractory nature of this syndrome[19]. Only 20% of patients improved on immunotherapies, while 37% remained stable. However, this might be linked to delayed treatment initiation, as exact data on time to treatment initiation is lacking in many cases. In analogy to other PNS[43], immunotherapy should be started early, as exemplified by the different disease course of our two cases. The immunotherapeutic management in general is complicated by the low evidence grade with only few prospective studies concerning the therapeutic approaches of PNS[44]. Many patients need a second-line immunotherapy, which is often chosen on a trial-error basis or depending on other co-morbidities or age.

Several limitations of this comprehensive review have to be acknowledged. All literature to KLHL11-IgG is based on case reports or case series, which are generally considered low level evidence. While tabulating the data especial attention was paid on not duplicating the cases, when they had been published twice by the same centre, but duplication of a few cases cannot be ruled out. A few of the case series were also based on retrospective testing for KLHL11-IgG among patients with different neurological presentations or already diagnosed with a well-es-

tablished neurological disease (e.g. anti-NMDAR encephalitis)[9,12]. A publication bias associated with case reports cannot be excluded, as often only new, atypical or distinctive presentations are reported. There was a large degree of heterogeneity in reporting details of the cases (e.g. in regard to symptoms vs. clinical syndrome, imaging details, antibody-titre and CSF-analysis). Since not all details were reported it was not possible to assume the clinical syndrome if it was not reported as such, what can lead to misrepresentation of the proportion of the clinical symptoms or syndromes. Also, underreporting of clinical or investigation findings cannot be excluded. Therefore, a prospective study design of KLHL11-IgG encephalitis also addressing the so far described refractory course of the disease (e.g. compared to other paraneoplastic antibodies) is imperative.

Conflicts of interest and Authors Disclosures

- Léon Betancourt A
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Author contributions

- **Léon Betancourt A:** writing – original draft (lead), conceptualization, formal analysis, methodology (lead), literature review/investigation (lead), revision of the manuscript.
- **Friedli C:** writing – original draft (supporting), conceptualization, methodology, supervision, review and editing of the manuscript (equal).
- **Sabater L:** visualization (cell based images), review and editing
- **Salmen A:** review and editing
- **Hoepner R:** review and editing
- **Oberholzer M:** review and editing
- **Millonig A:** review and editing
- **Diem L:** review and editing
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