

Practical Neurology: Test yourself:

A diagnostic conundrum

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Word count: 1490

Tables: 2

Figures: 4

References: 3

Funding: AMR is funded by a Wellcome Trust Postdoctoral Fellowship for Clinicians (110043/Z/15/Z)

Conflicts of interest: None

Abstract

We present a 26 year old male with a 6 year history of painful sensory symptoms, weakness and wasting in the legs alongside progressive facial weakness, slurred speech, dysphagia and ophthalmoplegia. There were no neurological symptoms or signs in the upper limbs.

Previous medical history included traumatic corneal injury to the left eye in childhood and a cisterna magna choroid plexus papilloma which was removed surgically at age 22.

Investigations localised the pathology to the cranial nerve and pre-ganglionic lumbar nerve roots. A dural meningeal biopsy demonstrated grade 1 choroid plexus papilloma, 4 years after presumed curative excision of the original lesion. This presentation with multifocal peripheral nervous system deficits is due to choroid plexus papilloma drop metastases.

We summarise the case and discuss the significance of the neurophysiology and imaging findings contributing to diagnosis.

Presenting complaint

A 26 year old patient was referred with facial weakness, dysarthria, dysphagia, ophthalmoparesis and severely weak and wasted legs.

Symptoms began aged 20 with electric-shock pains and paraesthesia in both feet progressing to the lower calves over 6 months. He then developed buttock numbness and occasional faecal incontinence. By age 22, he had diffuse lower limb weakness and wasting, with difficulty standing from a seated position and frequent tripping. He became wheelchair dependent within 3 years.

Over the same time period he developed progressive facial weakness, bilateral ptosis, slurred speech, difficulty chewing and swallowing, and lost 10kg of weight. He complained of hearing difficulty, and an audiogram demonstrated high frequency hearing loss. Important negatives included absence of upper limb symptoms, autonomic, cardiac, respiratory or cognitive dysfunction.

He was from a non-consanguineous, Lithuanian background and the eldest of 3 siblings. He was born following a normal pregnancy and delivery, and motor development was normal.

He had a left corneal abrasion with visual impairment following an accidental chemical injury aged 14. During the initial investigation of his symptoms (age 23), a choroid plexus lesion in the fourth ventricle was found. It was completely resected and histology confirmed benign choroid plexus papilloma (CPP), WHO grade I. Post-operative neuro-oncology discussion deemed the lesion cured.

Examination

He had bilateral ptosis, bilateral facial wasting, and could not close his mouth against gravity (Figure 1a). Visual acuity was reduced to perception of light on the left, 6/9 on the right. There was almost complete, complex ophthalmoplegia (Figure 1b) without fatigueability. Trigeminal sensation was reduced. He could not achieve eyelid closure; frontalis, buccinator and orbicularis oris were symmetrically weak. Speech was dysarthric and tongue was weak. Uvula was central with symmetrical palatal movement, but gag reflex was reduced.

Tone, power, muscle bulk, reflexes and sensation were normal in the upper limbs. There was marked wasting of lower limb muscles with flat feet (Figure 1b) and global, slightly asymmetrical weakness with 3/5 hip flexion power bilaterally compared to 4- in extension, knee flexion 4- bilaterally, knee extension 4 on the right, 4+ left, ankle dorsiflexion 0 on the right, 3 left, and plantar flexion 4 bilaterally. Tone was normal and reflexes were absent with flexor plantaris. He could just stand from the chair with assistance and take a few independent steps with trendelenberg gait and foot drop.

He had reduced pinprick sensation to mid-shin on the right, ankle on the left. Vibration was reduced to the costal margins; joint position absent at the hips.

Q1 How would you anatomically localise the pathology and what would be the most helpful first test?

Complex ophthalmoplegia can be due to ocular myopathy, myasthenia, multiple cranial neuropathies or brainstem disease affecting conjugation pathways. Facial weakness (involving frontalis) with wasting implies lower motor neuron pathology. Sensory deficit involving of cranial nerves CNV and VII excludes myopathic and neuromuscular junction disorders so the pathology must involve multiple cranial nerves.

The pattern of sensory disturbance and weakness in the lower limbs developed in a non-length dependent fashion, affecting the dorsum of the feet and anterior shins (L4/5) and buttocks (S3/4) sequentially. Weakness and sensory loss to above the knees without upper limb involvement is incompatible with a length-dependant peripheral neuropathy and suggests polyradiculopathy.

Neurophysiology including nerve conduction studies (NCS) and electromyogram (EMG) would be the initial investigation of choice (Table 1).

Q2 How would you interpret the neurophysiology?

The facial nerve and lower limb motor studies show markedly reduced compound muscle action potentials (CMAPs) consistent with axonal damage. Conduction velocity is slow due

to loss of the large, fast-conducting fibres rather than demyelination. The EMG changes are unequivocally neurogenic; large Motor Unit Action Potentials (MUAPs) and increased recruitment are consistent with chronic denervation with re-innervation. Muscle fibrillations indicate active denervation. Both proximal, (vastus medialis) and distal (gastrocnemius) muscles were equally involved compatible with a non-length dependant process. The upper limbs were completely normal.

Sural Sensory Nerve Actions Potentials (SNAPs) were normal, but clinically sensation was severely affected. This suggests a pre-ganglionic lesion; a lesion to the sensory spinal nerves proximal to the dorsal root ganglia, located in the posterior spinal nerves roots of the intervertebral foramina, very close to the spinal cord. If the dorsal root ganglion is spared, the distal nerve does not undergo Wallerian degeneration and SNAPs appear normal, despite the patient having severe sensory loss. In postganglionic lesions, SNAPs are reduced in the distribution of the sensory disturbance. This allowed for localisation of the lesion to a multi-level lumbar radiculopathy with proximal pathology (Figure 2).

Q3 What is the differential diagnosis of this patient's condition?

The combination of complex external ophthalmoparesis, ptosis, hearing loss, weight loss and limb weakness could be explained by mitochondrial disease (CPEO-plus). But myopathic pathology would typically involve all four limbs and is incompatible with the neurogenic EMG. The sensory involvement and absence of fatigability makes myasthenia unlikely. The presentation is too slow for Fisher syndrome. Chronic ataxic neuropathy with ophthalmoplegia, IgM band, cold agglutinins and disialosyl antibodies (CANOMAD) was considered until an IgM band was excluded. Sarcoidosis can also present with multiple cranial neuropathies and the myopathy can appear neurogenic on EMG.

The differential diagnosis for this unusual presentation is given in Table 2.

Q4 What would you do next?

On the basis of this differential diagnosis a number of blood tests were performed.

FBC, ESR, CRP, liver function and renal profile were normal; CK=219 IU. B12 and folate were normal; plasma homocysteine= 13.9 umol/L (5-12), Methylmalonate = 0.12 umol/L (0-0.28). Rheumatologic /vasculitic screen were normal or negative. Infection screen including HIV, Lyme, hepatitis and syphilis serology were negative. TB culture was negative on blood and CSF. AChR, MuSK, Ganglioside and antineuronal antibodies were negative. Immunoglobulins were normal. There was no evidence of a paraprotein in serum or urine on immunofixation. Cerebrospinal fluid (CSF) analysis was performed on 3 occasions; all of which were technically difficult and exquisitely painful for the patient. RBC counts were $>10,000/\text{mm}^3$ with protein of $>6\text{g}$. WCC 380/microliter (lymphocytes=377); glucose= 3.7 g/L , 6.0g/L in serum. Cytology revealed heavily blood stained samples but no atypical cells.

A muscle biopsy was performed early in the clinical course, at age 23, and showed grouped fibre atrophy with occasional vacuoles and a few internal nuclei. No mitochondrial abnormalities were seen. Chest xray and CT chest was normal. CT PET scan showed uptake in a buttock pressure sore but was otherwise normal.

MR imaging of the neuroaxis performed age 23 revealed a lesion in the fourth ventricle (Figure 3a, b). Review of the original histology confirmed a WHO grade 1 choroid plexus papilloma and post-operative imaging was reassuring for complete resection of the mass. Retrospective examination of the spinal imaging from that time was interesting because of leptomeningeal irregularity at L3/4 (Figure 3c,d) with "sugar-coated" appearance on the post-gadolinium sequences.

Repeat brain and spine MRI performed 3 years later showed no recurrence of the fourth ventricle lesion, but thickening of vestibular cranial nerves (Figure 3d,e) and progressive nodular thickening of the cauda equine.

Q5 What is the significance of the thickened nerve roots on MRI?

Nerve root thickening is commonly seen in inflammatory neuropathy such as AIDP/CIDP, but should be interpreted in the context of the history, examination and neurophysiology.

Pathological enhancement of the nerve roots with gadolinium is found in infiltrative conditions such as lymphoma . Arachnoiditis, which is a broad term encompassing inflammation of the meninges and subarachnoid space, can give a similar appearance. This is seen in infectious meningitis, granulomatous disease, iatrogenic (post-surgery, intrathecal

bleeding or after multiple lumbar punctures) or part of a malignant process such as carcinomatous meningitis or as “drop” metastasis from primary CNS tumours. This phenomenon has been described in multiple tumour types including CPP; tumour particles spread via cerebrospinal fluid pathways forming well differentiated tumours at other sites without malignant transformation of the primary. Local spread and gravitation deposition at the cauda equina with a sugar-coating appearance of the leptomeninges on imaging is characteristic.

Q6 How would you confirm the diagnosis?

Three high volume CSFs for cytology, have a sensitivity of >99% in the diagnosis of carcinomatous meningitis. CSF cytology in this case was uninterpretable due to blood staining despite good lumbar puncture technique with image guidance. In a progressive, generalised neurogenic process, nerve biopsy can be helpful but with the clinical, neurological and radiological evidence pointing to a proximal pathology, a sural nerve biopsy would not have been indicated here. A good rule of thumb is only to biopsy a clinically affected sensory nerve with an absent or severely reduced sensory action potential. A targeted intradural lumbar meningeal biopsy was performed. This demonstrated WHO grade I choroid plexus papilloma (CPP) (Figure 4b) providing histological confirmation of metastatic CPP, encroaching upon the local cranial and lumbrosacral nerve roots. The patient was planned for local cranio-spinal radiotherapy to the affected areas

Discussion

Choroid plexus papillomas (CPPs) are rare, making up only 0.4% of adult intracranial tumours with a mean age of presentation of 31 years and male predominance. Paediatric CPPs occur in the lateral ventricles but in adults fourth ventricular lesions are more frequent (Ahn & Cho, 2007). CPPs are considered benign lesions with a favourable prognosis (McEvoy, Galloway, Revesz, & Kitchen, 2002) and complete surgical removal is generally curative (Ahn&Cho, 2007). The commonest complication is hydrocephalus but spread by leptomeningeal seeding or gravitationally disseminated spinal ‘drop metastasis’ is well recognised. In individual case reports radiotherapy or chemotherapy with alkylating agents such as lomustine have been used in addition to total or sub-total tumour resection when

extensive metastases are evident at presentation. Predictors of recurrence related to the extent of surgical resection, radiological and immunohistochemical findings have been suggested but information is limited by small numbers and short follow-up. (Safaei et al., 2013) Reviewing 20 cases of drop metastasis of CPPs from 1980-2012 reveals prognosis is variable (mortality at 2 months to stable at 4 years), and likely related to location, extent of disease and treatment.

Learning Points

1. Determining genetic vs acquired aetiology in young patients can be difficult. Understanding the length of history and speed of progression is extremely useful in making this differentiation.
2. In a young patient, the likelihood of two unrelated rare pathologies co-existing but unrelated is very low.
3. Careful anatomical localisation is the key to appropriate and informative investigations.
4. Benign tumours can have disabling consequences.

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Table 1 Nerve conduction studies and EMG preformed age 26.

Mixed nerve conduction studies	Right	
	μV	<i>m/s</i>
Radial (forearm-snuffbox)	43	60
Median (D3-wrist)	23	62
Superficial peroneal	13	50
Sural (calf-ankle)	12	51

Motor nerve conduction studies	DML (ms)	CV (m/s)	CMAP (mV)	Minimal F-wave latency
	<i>ms</i>	<i>m/s</i>	<i>mV</i>	<i>ms</i>
Median (SE on APB)	3.6	59	7.0	30
Common Peroneal (SE on EDB)	no response	no response	no response	no response
Tibial (SE on AH)	5.5	35	0.1	absent
Tragus – frontalis	8.4		0.2	

EMG	Spontaneous activity		MUAP configuration			Recruitment	Interference
	Fibs/PSW	Other	Duration	Amp	Polyphasic		
L Deltoid	0	0	N	N	N	N	N
L Flexor Carpi Radialis	0	0	N	N	N	N	N
R Vast Med	2+	CRD	↑↑	↑↑	↑↑	Reduced, large units recruiting early	↓
R Gastroc (mh)	2+	CRD	↑↑	↑↑	↑↑	Reduced, large units recruiting early	↓↓

Table 2 Differential diagnosis

Inherited	Acquired
Systemic amyloidosis – Agel (Gelsolin amyloidosis: <i>GEL</i>)	CANOMAD (Chronic Ataxia Neuropathy, Ophthalmoplegia, IgM paraprotein, cold Agglutinins, Disialosyl antibodies)
Brown-Vialetto-Van Laere syndrome (<i>SCL52A2</i> or <i>SCL52A3</i>)	Meningitic infiltration- Lymphoma, TB, basal skull granulomatosis, sarcoidosis, bechet's
Facial Onset Sensory Motor Neuronopathy (associated with <i>TDP43</i>)	AL amyloidosis
Tangier's (<i>ABCA1</i>)	Sjogren's

Figure legends

Figure 1 Clinical examination at age 26. Photographs provided by the patient demonstrate degree of facial (a) and lower limb (b) wasting. Diagrammatic representation of ophthalmoparesis is shown in (c).

Figure 2 Anatomy of pre and post-ganglionic pathology

Figure 3 MRI imaging. Sagittal FLAIR (a) and post-gadolinium axial T1w (b) images of the brain, show a mildly enhancing, FLAIR hyperintense extra-axial lesion (*) centred on the fourth ventricle.

Sagittal T2w (c) and post-gadolinium sagittal T1w (d) images of the thoracolumbar spine show nodularity and enhancement along the distal spinal cord and cauda equina.

High resolution T2w (e) and post-gadolinium coronal T1w (f) images at the level of the internal auditory canals, demonstrate nodularity and enhancement (arrows) relating to the 7th and 8th nerve complexes bilaterally.

Figure 4 Histology from fourth ventricular (resected age 23) and lumbar spine lesion

(resected aged 26). Low power view of the resected lesion from the fourth ventricle foramen magnum (a) and lumbar intradural biopsy (c) showing a papillary neoplasm with identical appearances. High power view images of the fourth ventricle (b) and lumbar intradural (d) lesions demonstrating delicate fibrovascular tissue cores lined by a single layer of epithelial cells with inconspicuous mitotic activity, absent nuclear pleomorphism and no necrosis.