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Case study

Acquired sensorimotor polyneuropathy in an adolescent boy with primary intracranial sarcoma

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ABSTRACT

Acquired polyneuropathies (PN) are rare in childhood and adolescent. We report on a 15-year-old male patient who presented with progressive gait instability, ataxia, neuropathic pain, distal muscle weakness and progressive loss of ambulation. Nerve conduction studies (NCS) revealed a progressive demyelinating sensorimotor polyneuropathy predominantly of the lower limbs. Cerebrospinal fluid (CSF) analyses revealed a cytoalbuminologic dissociation. Extensive diagnostic workup for autoantibodies and inflammatory markers was inconclusive. Corticosteroids and intravenous immunoglobulins did not affect. Cranial MRI revealed leptomeningeal enhancement of the cerebellum and the brainstem. Brain biopsy of the cerebellar lesions revealed an unclassifiable sarcoma. The patient was treated according to the CWS guidance study resulting in a decrease in enhanced lesion size. After two years NCS still revealed a demyelinating sensorimotor PN. This case report describes for the first time the clinical course of a chronic PN, putative paraneoplastic, associated with isolated unclassifiable CNS-sarcoma in an adolescent patient. Paraneoplastic pathogenesis should be considered in an unusual sequence of subacute progressive neurological symptoms even in children and adolescents.

1. Introduction

Acquired polyneuropathies (PN) are a rare disease entity in pediatric patients. Differential diagnoses include acquired causes such as toxin-induced and vitamin deficiency, but also tumours compressing the myelon.

A more common cause of acquired PN in children are the sensorimotor neuropathies, such as Guillain-Barré syndrome

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(GBS) or, in case of prolonged progression longer than eight weeks, chronic inflammatory demyelinating polyneuropathy (CIDP). GBS is a reactive, autoimmune disease triggered by a previous bacterial or viral infection, immune reactions against myelin result in acute inflammatory demyelinating neuropathy.

A very rare cause of PN is the paraneoplastic neurological syndrome (PNS), which can affect any part of the nervous system including motor neurons, sensory ganglia, nerve roots, plexuses, cranial and peripheral nerves and neuromuscular junctions.[1] By definition, PNS is not caused by direct tumour infiltration or metastasis, vascular, metabolic, infectious or therapy-induced tumour complications.[1] According to Graus et al. PNS can be divided into "definite" and "possible" PNS, based on the presence of cancer, well-characterized onconeural antibodies, therefore antibodies against neuronal antigens expressed by the tumour, and the classification of classical versus non-classical neurological syndrome.[2] The latter is subdivided regarding the area of involvement: the central nervous system, peripheral nervous system, neuromuscular junction and muscle itself. The peripheral nervous system syndromes encompass subacute sensory PN, acute sensorimotor neuropathy (GBS or brachial neuritis), subacute or chronic sensorimotor polyneuropathies (CIDP), neuropathy and paraproteinaemia, neuropathy with vasculitis and autonomic neuropathies (chronic-gastrointestinal pseudo-obstruction, acute pandysautonomia). Only two of these disorders, subacute sensory PN and pseudo-obstruction, are classified as "classical".[2] ''Classical neurological syndromes'' per definition are often associated with cancer. Subacute sensory polyneuropathy is the most common type of peripheral nerve involvement and causes 24% of peripheral nervous system involvement in PNS.[1,2] In contrast, acute and chronic inflammatory polyneuropathy (CIDP) occurs in 1,6 and 1,3%, respectively and is classified as "non-classical syndrome".[1]

An estimated 6% of all pediatric malignant diseases are soft tissue sarcomas.[3] Isolated primary intracranial sarcomas are very rare in childhood with an estimated incidence between 0,1 and 4% of all intracranial tumours.[3,4] Reports on pediatric intracranial primary sarcomas are limited to single-case reports and small case series. Especially unclassifiable sarcomas seem to have an unfavourable prognosis.[4] CNS-sarcomas can occur at any age but are more likely to be found in children.[4] The radiomorphological pattern of primary brain sarcomas on MRI is non-specific.[4]

So far, possible PNS in pediatric or adolescent isolated CNS-sarcoma has not been described before.

2. Case study

The index patient is the first child of healthy non-consanguineous parents of Lebanese descent. At the age of 15-years, he presented with a four-week history of progressive gait instability, ascending paraesthesia, burning pain and tenderness on exertion for the lower extremities. Neurological examination revealed hyporeflexia, ataxia, predominant distal muscle weakness of the lower extremities and a mild upper limb involvement with slightly lowered reflexes and muscle strength. Furthermore, the patient showed a normal mental state, normal cranial nerve examination and the absence of clinical features of raised intracranial pressure. An elevated protein concentration of 1016 mg/L (NR < 450 mg/L) without pleocytosis (cyto-protein dissociation) was detectable in cerebrospinal fluid (CSF). The intracranial pressure (ICP) was normal. Nerve conduction studies (NCS) showed severely pathological results with missing motoric potentials of the lower extremities. Even though the widely used criteria for a demyelinating neuropathy (CV < 38 m/s) was not met, the results of the NCS suggest a demyelinating neuropathy due to longer latencies of the motoric and sensoric potentials with normal amplitudes (Table 1).

The reference values by Cai and colleagues were applied for the NCS analyses.[6] Based on the working hypothesis of GBS/CIDP the patient received two three-day courses of 2 g/Kg intravenous immunoglobulin (IVIG) at week six and eight following the onset of symptoms according to international treatment guidelines of pediatric GBS. There was no significant clinical change following this treatment, and the polyneuropathy progressed. Nine weeks after symptom onset, 1000 mg/d methylprednisolone was administered over three days. However, there was no subsequent clinical improvement, and the patient became a wheelchair user 12 weeks after onset.

Cranial and spinal MRI revealed leptomeningeal enhancement of the cranial nerves (V, VII, VIII, IX, X bilateral), cerebellum, brainstem, spinal nerves, spinal cord, and the cauda equina fibres (Fig. 2) of unknown origin without ventricle dilatation. No malignant cells were detected in CSF. Figs. 1 and 3.

Extensive testing including diagnostic panels for autoantibodies (see annex 1), vitamin deficiency and inflammatory and infectious markers were inconclusive. Brain biopsy of the cerebellar lesions, taken before methylprednisolone therapy, revealed histologic finding of "small blue round malignant cells" with histopathological and molecular features compatible with cerebral undifferentiated sarcoma. These characteristics are a strong expression of β-catenin and expression of beta III-tubulin and partially of synaptophysin. Proliferation marker Ki67 was express focally. Tumour cells expressed vimentin, CD99 (Mic-2) and also neural antigen Map2c, while glial fibrillary acidic protein (GFAP) was expressed by infiltrated tissue but not by the tumour cells. Accumulation of p53 could be found in 5% of the tumour cells. Inflammatory causes, in this case, were excluded.

According to the cranial MRI, the primary tumour probably was based on the arachnoid mater. Whole body MRI and lung CT showed no primary tumour and no metastases. According to the diagnostic criteria by Graus et al. a diagnosis of a "possible" PNS was applied because of the combination of a non-classical neurological syndrome, the absence of onconeural antibodies and cancer present within two years of diagnosis.[2]

Due to the diagnosis of a malignant brain tumour, the patient was treated according to the GPOH (Gesellschaft für pädiatrische Hämatologie Onkologie, Germany) CWS guidance study protocol NRSTS (Non-Rhabdomyosarcoma Soft Tissue Sarcomas) VAIA III High-Risk Group by polychemotherapy and craniospinal radiation for five months. The patient developed severe chemotherapy-associated toxic adverse effects including high-dose ifosfamide-

induced encephalopathy °III with somnolence, dizziness, and hallucinations, nephropathy with electrolyte deficits and cardiomyopathy likely to be related to anthracyclines. Thus protocol-based treatment was ceased. Following the advice of the CWS-Study-Group, the patient received a temozolomide-long-term therapy (150–200 mg/m^2 for five days) over a period of two years. Six weeks after radiation cranial MRI revealed a consistent left temporomesial enhanced residue and leptomeningeal enhancement at height T11/T12 without spinal metastases. The tumour lesions decreased incompletely.

One year after onset, NCS revealed no significant change with a complete absence of electroneurographic sensory and motor potentials of the lower extremities and marginal worsening of the upper extremities (Table 1). Due to great discomfort and pain of the patients during the NCS the stimulus intensity was not further increased when no change in amplitude or latency occurred. Based on unchanged NCS results and still existing tumour residuum one course of plasmapheresis was given without improvement.

During eight-month neurorehabilitation, the adolescent achieved a motor improvement. Initially, he was able to sit without support and then to stand with the help of auxiliary and walking aids. The patient was able to walk with splints and walking aids two years after symptom onset and 17 months after using a wheelchair. NCS two years after disease onset still revealed a sensorimotor polyneuropathy of the lower limbs with a complete absence of sensory and motor potentials (Table 1). Normal values of NCS were obtained in the upper extremities, which was consistent with the clinical-neurological findings. Three years after diagnosis of CNS-sarcoma cranial and spinal MRI continued to show an abnormal but decreased temporomesial and unchanged spinal enhancement.

Table 1 – Displayed are the NCS of the upper and lower extremities during the time course of the disease. Pathological values are displayed in light grey. Reference values for the NCS were used from Cai F, Zhang J et al. Study of Nerve Conduction and Late Responses in Normal Chinese Infants, Children, and Adults. *Child Neurol* 1997; 12: 13-18. CMAP: compound motor action potential; SAP: sensory action potential; DML: distal motor latency; CV: conduction velocity.

Date of examination	Four weeks after onset			Eight weeks after onset			1 year after onset			2 years after onset			3 years after onset		
motor	DML	CV	Amplitude	DML	CV	Amplitude	DML	CV	Amplitude	DML	CV	Amplitude	DML	CV	Amplitude
N. medianus left	3.5	46.7	9.2	3.7	44.8	12.1	5.0	43.3	4.0	3.1	56.9	11.9	3.2	54.3	11.6
N. ulnaris left	3.2	50.0	10.3	3.2	48.4	12.5	3.8	45.8	3.4	2.8	48.8	10.2	2.2	56.2	10.3
N. tibialis right	CMAP not detectable			CMAP not detectable			CMAP not detectable			CMAP not detectable			CMAP not detectable		
N. peroneus right	CMAP not detectable			CMAP not detectable			CMAP not detectable			CMAP not detectable			CMAP not detectable		
sensory	Latency	VC	Amplitude	Latency	CV	Amplitude	Latency	CV	Amplitude	Latency	CV	Amplitude	Latency	CV	Amplitude
N. medianus left	3.0	51.0	16.0	3.0	48.3	28.0	2.6	48.1	12.0	2.8	47.2	21.3	2.5	66.0	11.2
N. suralis right	2.8	47.0	3.1	3.8	34.7	1.1	SAP not detectable			SAP not detectable			SAP not detectable		

3. Discussion

PNS is very rare in childhood and almost exclusively associated with the opsoclonus-myoclonus syndrome in neuroblastomas. Other tumour entities are teratoma and Hodgkin lymphoma mainly associated with limbic encephalitis and anti-NMDA receptor encephalitis. The prevalence in children is unknown.[5]

In 18% of PNS, onconeural antibodies are not detectable.[1] An autoimmune-pathogenesis with co-reactivity of malignant tumour- and neuronal tissue-derived antigens is believed to be causative.[3] However, the direct effect of antibodies has not been proven.

To our knowledge, this is the first case report, describing a sensorimotor polyneuropathy in an adolescent patient with primary CNS-sarcoma.

In comparison to other descriptions of intracranial sarcomas[3,4] this case presented instead of space-occupying lesions with diffuse leptomeningeal infiltration. Thus, efforts were undertaken to confirm the diagnosis of a malignant process and to classify the tumour as sarcoma by two independent reference pathologists. No comparative data of cell surface marker expression in CNS biopsies from enhancing areas in GBS/CIDP is reported in the literature so far.

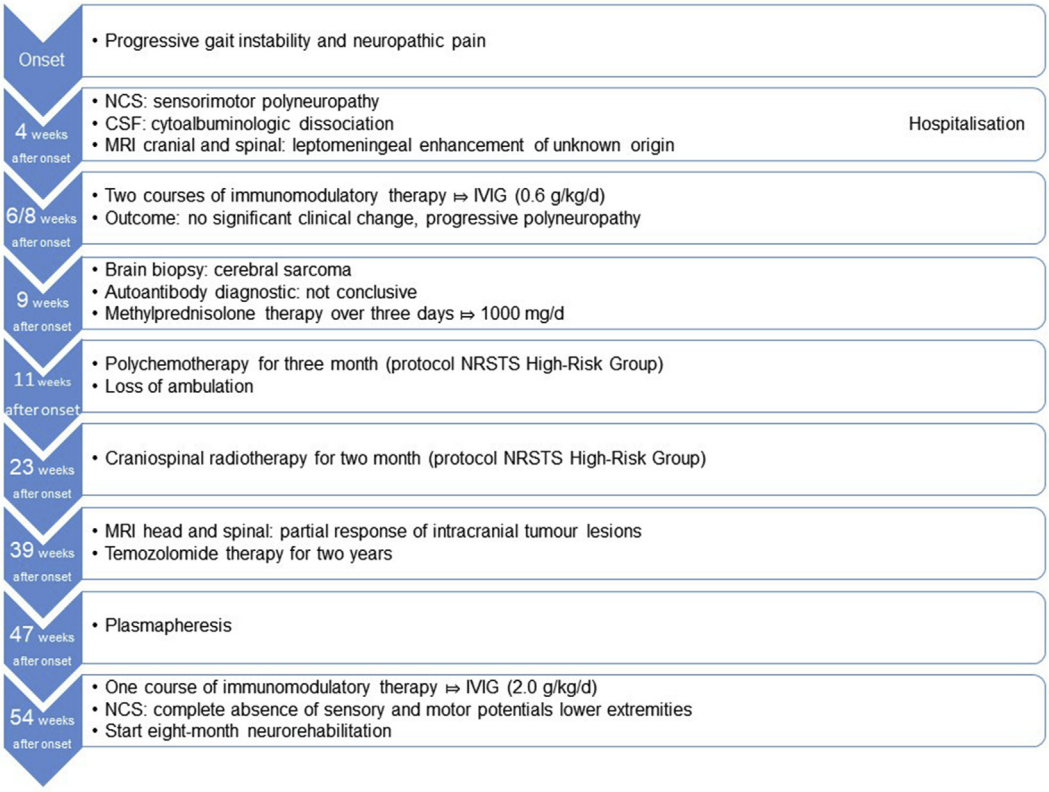

Fig. 1 – Diagnostic and treatment timeline. NRSTS: Non-Rhabdomyosarcoma Soft Tissue Sarcomas.

According to Graus and colleagues, diagnostic criteria for "possible PNS" comprises a non-classical neurological syndrome like sensorimotor PN, without onconeural antibodies and cancer present within two years from diagnosis. However, the diagnosis of PNS is just "possible" and not certain. A coincidence of GBS/CIDP and cerebral sarcoma is conceivable. All criteria of GBS/CIDP (symmetrical distal ascending muscle weakness, distal reflexes not releasable, NCS and CSF findings

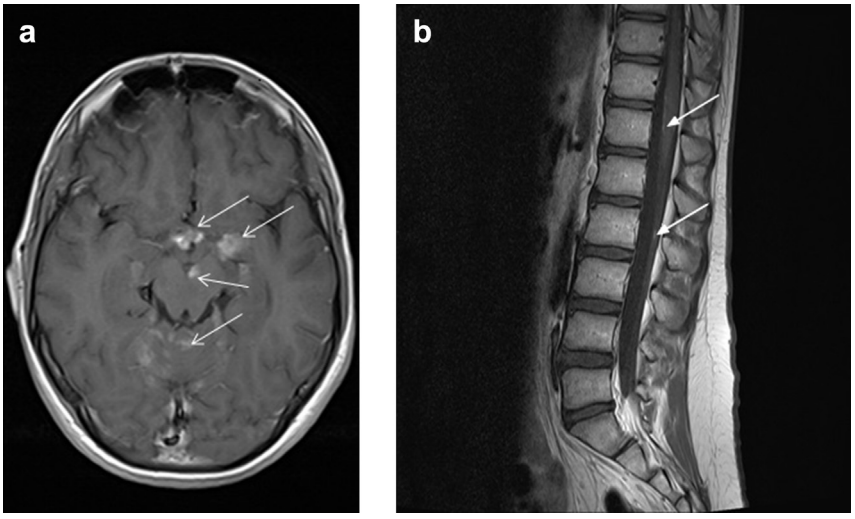

Fig. 2 – Cranial and spinal MRI at manifestation preceded by five weeks of progressive symptoms due to the polyneuropathy at the age of 15 years. (A) Cranial MRI (Siemens Avanto, 1,5 T; transversal T1-weighted images) after contrast medium application reveals a multifocal enhancement of the arachnoidea suprasellar, of the brainstem and the cerebellum (not shown the arachnoidal enhancement of the interhemispheric fissure, and at multiple temporal, temporomesial and frontal locations). (B) Spinal MRI (Siemens Avanto, 1,5 T, sagittal T1-weighted images) of the lumbar region after contrast medium reveals a multifocal enhancement of the arachnoidea of the spinal cord and the cauda equina fibres.

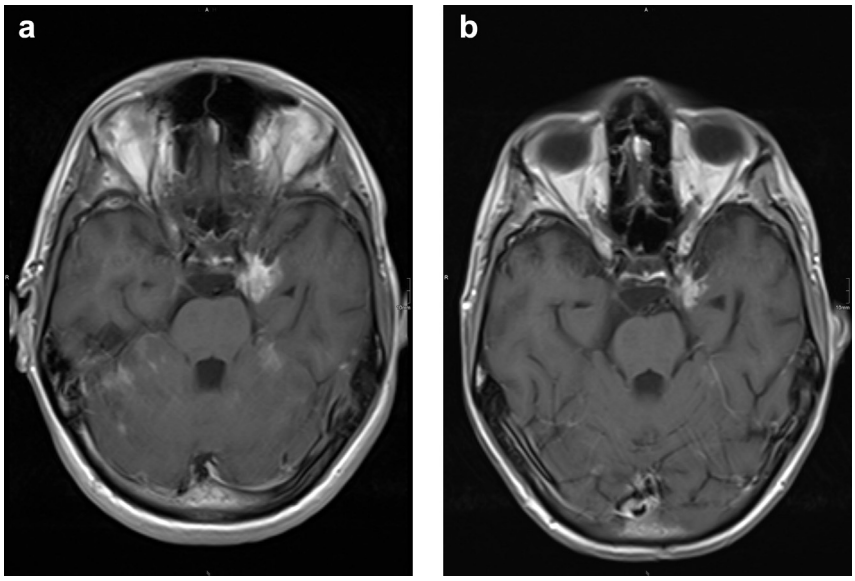

Fig. 3 – Cranial MRI of the temporomesial lesion. (A) Cranial MRI (Siemens Avanto, 1,5 T; transversal T1-weighted images) after manifestation. Contrast medium application reveals a temporomesial and multifocal enhancement (multifocal enhancement shown in Fig. 2). (B) Post-treatment cranial MRI three years after diagnosis (Siemens Avanto, 1,5 T; transversal T1-weighted images). Contrast medium application reveals a decreased temporomesial enhancement.

with cyto-protein dissociation, enhancement of the cauda equina) were verified. Nevertheless, GBS/CIDP is a diagnosis of exclusion and PNS a possibility. Moreover, GBS/CIDP itself can be a disorder of paraneoplastic origin, following Graus' diagnosis criteria. The acute onset, severe progress and long-term course in this patient appear exceptional. Whereas GBS is not known to be associated with onconeural antibodies, CIDP is associated with them only in particular tumour types.[2] Other causes of PN, like direct tumour infiltration or malignant spinal meningitis, would lead to increased ICP, meningeal irritation, cancerous cells in CSF and segmental sensory loss with radicular pain.

A reinforcing effect of chemotherapy on PN can be assumed as well, but only vincristine (VCR) within the drugs used for VAIA III is claimed to cause peripheral neuropathy. When the patient was diagnosed, he suffered already from NCS, but no deterioration of existing NCS or appearance of new symptoms was observed while ten doses of VCR (1.5 mg/sqm, maximal dose 2.0 mg) were applied without dose modifications.

The absence of onconeural antibodies, in this case, highlights the importance of Graus' diagnostic criteria, which state that PNS can be diagnosed without evidence of onconeural antibodies.[2]

A detailed investigation of tumour- and onconeural antibodies should be carried out on patients with suspected PNS. Undoubtedly, the treatment of the neoplasia has priority, although it remains unclear whether the treatment and concomitant immunosuppression of the underlying disease are effective against PNS.[1] Additional therapeutic options include immunomodulatory strategies like corticosteroids, immunoglobulin, and antiproliferative maintenance. Plasmapheresis may be considered. As there are presently no established treatment guidelines based on larger cohorts or even randomized controlled trials, therapeutic algorithms and decisions in paraneoplastic neuropathies in children continue to remain a challenge.

With this case report, we aim to highlight the paraneoplastic syndrome as a rare but possible differential diagnosis of acute and chronic inflammatory polyneuropathy in childhood. In the case of atypical medical history, the absence of preceding infection, typical antibodies and an ongoing progression, tumour screening is essential.

Declaration of interest

None.

Appendix

Annex 1: Antibody and Autoantibody diagnostic. Antibody Laboratory Bethel/Bielefeld. AB: Antibody; AG: Antigen; AAB: Autoantibody; ANA: Antinuclear Antibody.

GAD65, GAD67, NMDA receptor, GABAB receptor, AMPA receptor, Glycin receptor, LGI1, CASPR2, PNMA2 (Ma-2/Ta), atypical AB against intracellular AG and atypical neutrophil AB, VGKC-complex-antibody.

ANA, cANCA, Purkinje- and Podocyte nucleus AB, HU, Ri, Yo (PCA-1, PCA-2, PCA-Tr, Aquaporin 4 IgG AB, Gangliosid GM1 AB IgG/IgM, Gangliosid GM2 AB IgG/IgM, Gangliosid GM3 AB IgG/IgM, Gangliosid GM4 AB IgG/IgM, Gangliosid GD2 AB IgG/IgM, Gangliosid GD3 AB IgG/IgM, Gangliosid GT1a AB IgG/IgM, Gangliosid GT1b AB IgG/IgM, Gangliosid GQ1b AB IgG/IgM, Ma2/Ta AB, Amphiphysin AB, CV2 AB, AAB against neuronal nuclei, type 2: ANNA 2/Ri, AAB against

cytoplasmatic AG of Purkinje cells type 1, AAB against neuronal nuclei type 1: ANNA-1/HuD.

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