Case Report

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Anti-SOX1 Antibodies in a 3-Year-old Girl, Post-Varicella

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Abstract

Anti-SRY-related HMG-box gene 1 (SOX1) antibodies were initially described in adults with paraneoplastic neurological disorders, where they are considered high-risk onconeural autoantibodies. Only two pediatric cases of anti-SOX1 antibodies have been reported: a 17-year-old adolescent presenting with paraneoplastic limbic encephalitis due to Hodgkin lymphoma and a 12-year-old girl presenting with non-paraneoplastic encephalitis. We present a unique case of anti-SOX1 antibodies in a 3-year-old girl, post-varicella infection. Initially, she presented with ataxia and dysmetria, with subsequent reports from parents of urinary incontinence and significant behavior changes. Additionally, reflexes in the lower limbs were absent. Anti-SOX1 antibodies tested positive in both serum and cerebrospinal fluid. Oncological screening at presentation and a seven-month follow-up showed no malignancies. The patient exhibited favorable clinical progress without requiring treatment. At the seven-month follow-up, serum antibodies tested negative. This case report broadens the known clinical spectrum, being the first description of post-varicella anti-SOX1 antibodies.

Keywords

SOX1, encephalitis, autoimmune, child, chickenpox, Varicella Zoster virus

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Introduction

In 2005, the presence of anti-glial nuclear antibodies targeting Bergmann glia cells in the adult cerebrum was reported in patients with Lambert-Eaton myasthenic syndrome (LEMS) and small cell lung cancer (SCLC). Subsequently, the corresponding antigen was identified as the SOX1 protein in 2007.[1,2] SOX1 protein is encoded by the SRY-related HMG-box gene 1 (*SOX1*), a highly conserved gene, and functions as an important transcription factor in central nervous system development.[3-5]

In adults, anti-SOX1 antibodies are classified as onconeural autoantibodies. Following their initial association with LEMS and SCLC, gradually, anti-SOX1 antibodies were progressively observed in diverse patient populations, with connections to various neurological symptoms and cancer subtypes. Paraneoplastic manifestations include limbic encephalitis, cerebellar degeneration, and neuropathy.[6,7] Interestingly, anti-SOX1 antibodies were also found in patients with neurological disorders without an associated tumor.[8,9]

To date, only two pediatric cases of anti-SOX1 antibodies have been reported. The first involves a 17-year-old adolescent with paraneoplastic limbic encephalitis due to Hodgkin lymphoma, and the second concerns a 12-year-old-girl witch encephalitis, where oncological evaluation yielded negative results.[10,11] Here, we present a rare case of a 3-year-old girl with anti-SOX1 antibodies post-varicella, and no associated malignancy.

Case

A 3-year-old girl presented to her general practitioner with complaints of staggering and frequently stumbling over the past day. Neurological examination revealed ataxia and dysmetria without signs of meningeal irritation. Nystagmus was not observed, and reflexes were symmetrical. Additionally, she had skin lesions consistent with a recent varicella infection. Nine days before presentation, the patient had displayed typical skin lesions and had experienced a fever for seven consecutive days. However, at the onset of ataxia, she had been fever-free for one day. A past medical history was unremarkable, but

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the family history noted a maternal case of stroke due to cavernous malformation.

The patient was referred to secondary care, where intravenous Aciclovir treatment at encephalitis dose was initiated (500 mg/m^3 every 8 h). Brain CT scan revealed no anomalies, while CT angiography was not feasible due to technical issues. Complete blood count, serum electrolytes, renal and liver function, glucose, and C-reactive protein levels were all within normal range. Cerebrospinal fluid analysis (CSF) showed an unremarkable cell count, glucose, and protein. CSF was also tested for viral PCR, including herpes simplex type 1 and 2, and varicella-zoster, as well as a bacterial culture. Given the patient's report of abdominal pain, an abdominal ultrasound was performed, revealing several mildly enlarged lymph nodes scattered throughout the mesentery, with some discreetly inflamed small intestine loops. This imaging pattern could potentially indicate a general viral infection or mild enteritis. The clinical presentation was consistent with post-varicella ataxia. However, the following day, the parents also reported urinary incontinence and a remarkable change in the girl's behavior. She displayed significant irritability, anger, and defiance, to the extent that her parents mentioned not recognizing their daughter anymore, as she typically presents herself as timid, polite, and affectionate. These additional symptoms prompted a transfer to a tertiary care center.

Upon admission, the patient's vital signs were within normal range. She exhibited reluctance during examination and required repeated motivation. She was alert and oriented to time, place, and person. There were no signs of meningeal irritation and cranial nerve functions were intact. Notably, nystagmus was not observed. Muscle tone was normal, without any indications of rigidity or spasticity. Muscle strength was graded as 5/5 in all major muscle groups and no atrophy, fasciculations or involuntary movements were noted. Symmetrical deep tendon reflexes were elicited in the biceps, triceps and brachioradialis reflexes, while patellar and Achilles reflexes were found to be absent. Sensory examination showed no abnormalities. The patient displayed dysmetria during the finger-to-nose coordination test and her gait was observed to be wide-based and unsteady. Additionally, the Romberg test was positive. The patient had difficulty maintaining balance, both with eyes open and eyes closed. Furthermore, the cardiovascular, pulmonary, and abdominal examinations did not reveal any abnormalities.

Additional diagnostic tests included MRI of the brain and spinal cord, EEG, blood and urine tests, and lumbar puncture. Imaging results were normal, showing no signs of encephalitis, cerebellitis, or evidence for Guillain-Barré syndrome. The EEG displayed a normal pattern. Laboratory findings are presented in Table 1. Cerebrospinal fluid analysis did not reveal any oligoclonal bands. However, the research of intracellular antibodies using indirect immunofluorescence and line blot techniques returned positive results for anti-SOX1 antibodies in both serum and CSF, with a positive IgG index in CSF. No other intracellular or extracellular antibodies were detected. Additionally, IgM anticardiolipin antibodies were elevated. The viral PCR on CSF for herpes simplex type 1 and 2, as well as varicella-zoster, yielded negative results, leading to the discontinuation of Aciclovir treatment.

The patient showed favorable clinical progress, with notable improvement of ataxia, and her reflexes became elicitable again. Consequently, she was discharged from the hospital after a 5-day stay. Due to the potential association of SOX1 antibodies with paraneoplastic conditions, an ultrasound of the abdomen and radiography of the thorax were performed, both yielding unremarkable results. At the 4-month follow-up from initial presentation, a repeat test using the same methodological and laboratory approach confirmed SOX1 positivity in serum. However, at that time, IgM anticardiolipin antibodies were negative. At the 7-month follow-up, the patient continued to exhibit a positive clinical course, with no residual symptoms. An MRI of the abdomen and thorax demonstrated no evidence of neoplasms. Additionally, anti-SOX1 antibodies in serum were found to be negative.

Discussion

The initial presentation strongly suggested post-varicella acute cerebellar ataxia. However, the presence of additional symptoms of incontinence, behavioral changes and areflexia in the lower limbs raised concerns as they did not align with this diagnosis. Consequently, the differential diagnosis was expanded, and further investigations were conducted. The potential diagnoses considered included Guillain-Barré syndrome, polyneuropathy, encephalitis, acute disseminated encephalomyelitis, central nervous system infection, traumatic brain injury, stroke, posterior fossa tumor or metabolic disease. None of these conditions were supported by the additional tests. Unexpectedly, SOX1 antibodies were detected. Accordingly, we can only confirm the diagnosis of acute cerebellar ataxia, post varicella, as the most likely cause of the patient's symptoms. No toxicological screening was performed. It's worth noting that IgM anticardiolipin antibodies were transiently positive, likely attributed to an inflammatory response. The increase in creatinine was also transient, potentially due to Aciclovir treatment.

Anti-SOX1 antibodies were detected in both CSF and serum, with the CSF showing a weakly positive result and serum displaying a moderately positive result. It's essential to mention that CSF tests were conducted on 1/2 diluted sample due to limited availability. The strongly positive IgG index suggested intrathecal IgG production. After a 4-month period, the antibodies remained weakly positive in serum, but at 7 months, they were undetectable.

Anti-SOX1 antibodies were initially described in adults in the context of paraneoplastic neurological disorders (PND). In this population, these antibodies are considered high-risk, with a cancer frequency exceeding 90%. However, PND are extremely rare in children.[12,13] SCLC, the tumor most strongly associated with anti-SOX1 antibodies in adults, is exceptionally uncommon in pediatric cases.[14] As this is only the third reported pediatric case with SOX1 antibodies in the literature, there are currently no established guidelines for further follow-up in such cases.

To address the possibility of an oncological etiology, we performed an initial oncological screening including clinical examination, blood samples, chest x-ray, and abdominal ultrasound. Since the paraneoplastic phenomenon can precede the oncological process, we repeated the screening seven months after the

Table 1. laboratory Findings.

CSF day 1		**Reference**			**Reference**
PCR HSV 1	Neg	Neg	Intracellular Ab		
PCR HSV 2	Neg	Neg	Screening*	Pos	Neg
PCR VZV	Neg	Neg	Anti amph	Neg	Neg
Blood Day 4			Anti CV2	Neg	Neg
Hematology			Anti PNMA2	Neg	Neg
WBC	10,68 ×10E3/µL	6–15	Anti Ri	Neg	Neg
Ne	67,6%	39,2–71,5	Anti Yo	Neg	Neg
Ly	17,9%	18,9–47,1	Anti Hu	Neg	Neg
Mo	10,8%	4,8–11,5	Anti recov	Neg	Neg
Eo	3,0%	0,4–5,9	Anti SOX1	Pos ++	Neg
Ba	0,3%	0,2–1,4	Anti titine	Neg	Neg
Hgb	13,0 g/dL	11,0–14	Anti Zic4	Neg	Neg
MCV	82,5 fL	73–85	Anti GAD65	Neg	Neg
PLT	435 ×10E3/µL	229–533	Anti Tr	Neg	Neg
Coagulation			Anti-gangl IgG	Neg	Neg
LA	negative		Anti-gangl IgM	Neg	Neg
ACA IgG	4 U/mL	<20	**CSF day 4**		
ACA IgM	59,5 U/mL	<20	TP	34,0 mg/dL	15–50
Hormon			Glu	68 mg/dL	49–80
TSH	1,2 mU/L	0,70–6,0	Lact	1,22 mmol/L	1,1–2,8
FT4	1,6 ng/dL	1,0–1,8	Alb	15,4 mg/dL	10–35
Biochemistry			IgG	7,5 mg/dL	0,3–4
CR	0,7 mg/dL	0,31–0,47	IgM	1,5 mg/dL	0–0,13
Alb	44 g/L	35–52	IgA	<0,3 mg/dL	0,08–0,5
AST	28U/L	11–50	IgG index	2,03	0–0,7
ALT	13 U/L	7–31	WBC	22/µL	0–8
CRP	3,8 mg/L	<5,0	RBC	13537/µL	0
IgG	10,3 g/L	4,7–9,3	CSF IEF	No OB	Neg
IgM	1,45 g/L	0,27–0,57	Intracellular Ab		
IgA	0,74 g/L	0,41–0,91	Screening*	Neg	Neg
IgE	4250 kU/L	0–60	Anti amph	Neg	Neg
C3	1,0 g/L	0,9–1,8	Anti CV2	Neg	Neg
C4	0,33 g/L	0,10–0,40	Anti PNMA2	Neg	Neg
NH3	23 µmol/L	21–50	Anti Ri	Neg	Neg
Urine day 4			Anti Yo	Neg	Neg
WBC	1,0/µL	0–25	Anti Hu	Neg	Neg
RBC	0,4/µL	0–25	Anti recov	Neg	Neg
Bacteria	6,9/µL	0–3858	Anti SOX1	Pos (+)	Neg
A1M	<3,5 mg/L	0–8	Anti titine	Neg	Neg
Nitrite	neg.	Neg	Anti Zic4	Neg	Neg
Auto-imm			Anti GAD65	Neg	Neg
ANA			Anti Tr	Neg	Neg
FP	Nucleolar		Extracellular Ab		
Intensity	1+	Neg	Anti NMDA R	Neg	Neg
Screening	Neg	Neg	Anti AMPA1 R	Neg	Neg
Anti-dsDNA	Neg	Neg	Anti GABAb R	Neg	Neg
ANCA			Anti CASPR2	Neg	Neg
FP	Atypical	Neg	Anti LGI1	Neg	Neg
Intensity	1+	Neg	Anti-gangl IgG	Neg	Neg
PR3 ELISA	0,8 IU/mL	<5: Neg	Anti-gangl IgM	Neg	Neg
PR3 ELIA	<0,7 IU/mL	<5: Neg			
MPO ELIA	<0,3 IU/mL	<5: Neg			

* For neural antibody detection, we used indirect immunofluorescence on monkey brain sections (Neurology mosaic-1; Euroimmun, Lübeck, Germany) and a line assay (Euroline PNS 12 Ag; Euroimmun, Lübeck, Germany). In case of a positive assay, the result is determined through colorimetric analysis. The measured color intensity is then converted into a semi—quantitative result. Intensity levels ranging from 0 to 5 are categorized as 0, 6 to 10 as (+), 11 to 25 as +, 26 to 50 as ++, and 51 to 255 as +++.

Abbreviations: A1M, α_1-microglobulin; ACA, anti-Cardiolipin antibodies; AI, auto-immune; Alb, albumin; ALT, alanine transaminase; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasm antibodies; AST, alanine aminotransferase; Ba, basophils; C3, complement C3; C4, complement C4; CR, creatinine; CRP, C-reactive protein; CSF, cerebrospinal fluid; dsDNA, double stranded DNA; ELISA, enzyme-linked immunosorbent assay; Eo, eosinophils; FP, fluorescence pattern; FT4, free thyroxine; Gangl, ganglioside; Glu, glucose; Hgb, hemoglobin; HSV, herpes simplex virus; IEF, isoelectrofocusing, IgA: immunoglobulin A, IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M, LA, lupus anticoagulant; Lact, lactate; Ly, lymphocytes; MCV, mean corpuscular volume; Mo, monocytes; MPO, myeloperoxidase; Ne, neutrophils; Neg, negative; NH3, ammonia; OB, oligoclonal bands; PCR, polymerase chain reaction; PLT, platelet count; Pos, positive; PR3, proteinase 3 antibody; R, receptor, RBC, red blood cell count; RBC, red blood cell; Recov, recoverine; TP, total protein; TSH, thyroid stimulating hormone; VZV, varicella zoster virus; WBC, white blood cell count.

disease onset, this time incorporating MRI of the thorax and abdomen. All examinations yielded unremarkable results. Moreover, at that time, the anti-SOX1 antibodies spontaneously became negative, which is not expected in a paraneoplastic setting without tumor removal, but more likely seen post viral infection. As a result, an oncological etiology seems unlikely, and we postulate that the autoantibodies arose post-varicella infection. This is supported by the presence of other autoantibodies that have been previously described post-varicella. However, a causal relationship between SOX1 antibodies and the patient's presentation cannot be established. It is possible that SOX1 is merely a bystander or unrelated to the patient's current condition.[15–18]

Similar occurrences of auto-immune neurological symptoms in childhood after viral infections have been observed, even when associated with autoantibodies known to be paraneoplastic in adulthood. For instance, anti-N-methyl-D-aspartate receptor antibodies were initially described in adults in a paraneoplastic context of encephalitis associated with ovarian teratomas. However, over time, these antibodies were also identified in children, particularly in prepubertal children, where underlying tumors are rare, and the antibodies likely occur post-viral.[19]

In summary, we present the youngest known case to date of a pediatric patient with SOX1 antibodies. This case report expands the known clinical spectrum, representing the first description of post-varicella anti-SOX1 antibodies.

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Author Contribution(s)

Wijnand, A: contributed to the conception and design contributed to the acquisition, analysis, and interpretation drafted manuscript Select item. Gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.
Verhelst, H: contributed to the conception and design contributed to analysis and interpretation Select item Critically revisited the manuscript for important intellectual content gave final approval Select item.

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