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Case Report

Subacute encephalitis in a child seropositive for alpha-3 subunit of neuronal nicotinic acetylcholine receptors antibody

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Abstract. A previously healthy and developmentally normal 5-year-old boy from Saudi Arabia presented with a 3 mo history of abnormal behavior in the form of hyperactivity, decreased social engagement, episodic aggressiveness, decreased cognitive performance in school, inappropriate laughter and talking to himself, insomnia, tics and other stereotyped behaviors. His clinical neurological examination did not reveal any focal neurological deficits, but a prolonged electroencephalogram showed non-specific slowing over the right hemisphere. A diagnosis of encephalopathy was entertained, and he underwent testing for infectious, toxic, metabolic and mitochondrial disorders. Magnetic resonance imaging of the brain and cerebrospinal fluid studies were all normal. However, a comprehensive evaluation of paraneoplastic antibodies from cerebrospinal fluid demonstrated the presence of antibodies against the alpha-3 subunit of the neuronal nicotinic acetylcholine receptor, a finding also documented by tests from two different laboratories. An extensive diagnostic investigation that included a fludeoxyglucose-positron emission tomography scan for malignancies showed negative results. The patient was treated with plasmapheresis treatments (five exchanges) that resulted in a significant improvement in his clinical picture. Following his initial treatments, the patient continued to receive monthly infusions of intravenous immunoglobulin. An evaluation at 5.5 mo after initiation of first treatment revealed a considerable improvement of his behavior and language abilities. The patient returned to his school where he has performed satisfactorily. To our knowledge, this is the first report of a child who developed sub-acute cognitive and neurobehavioral regression in association with the presence of a serum antibody to a neuronal ganglionic nicotinic acetylcholine receptor and who improved after immunotherapy.

Keywords: Neuronal nicotinic acetylcholine receptor antibody, paraneoplastic neurological disorder, encephalopathy, plasmapheresis

1. Introduction

Neuronal nicotinic acetylcholine receptors (nAChR) are widely distributed in both the nervous system and in non-neuronal tissues where they act as cationic channels controlled by the endogenous

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neurotransmitter acetylcholine or exogenous ligands like nicotine. These receptors are found on presynaptic or pre-terminal sites where they modulate neurotransmitter release or in dendrites where they modulate postsynaptic effects. In the central nervous system, acetylcholine mediates innervations via nAChR which regulate cell excitability and neuronal integration. Acetylcholine influences arousal, sleep, anxiety, satiety and cognitive functioning and is also essential for neuronal survival. The activity of these receptors is crucial in early pre- and perinatal neuronal circuit formation as well as age-related cell degeneration [1]. Eleven genes corresponding to the neuronal nAChR subunits (a2–a7, a9–a10, b2–b4) have been identified in the mammalian genome [2]. The most extensively expressed subtype of neuronal nAChR is the a3–b4 subunit which is highly expressed in autonomic ganglia and superior cervical ganglion, but also found in substantia nigra, striatum, hippocampus, locus coeruleus, habenulo-interpeduncular tract, cerebellum as well as pineal and adrenal glands [3]. The presence of autoantibodies against the neuronal ganglionic nAChR may lead to disruption of cholinergic synaptic transmission in autonomic ganglia that is responsible for dysautonomia symptoms. Detection of antibodies against nAChR is of diagnostic value for neurological disorders suspected to be autoimmune in nature or associated with paraneoplastic disorders [4]. The autoantibody specific for the alpha-3 subunit of the neuronal ganglionic nAChR, has been classically associated with idiopathic or paraneoplastic dysautonomia [5,6] and neoplasms such as thymoma and small cell lung carcinoma [7]. McKeon et al. [8] found the association of this autoantibody with a wide variety of neurological manifestations, including peripheral neuropathy and central nervous system disorders in adult patients with diverse types of malignancy, the most common being adenocarcinoma.

In this report, we describe a 5-year-old child who presented with sub-acute changes in behavior and personality, which primarily presented as neuropsychiatric symptoms including decreased socialization and isolated behavior, self-talking, hyperactivity, inappropriate laughter, visual hallucinations and insomnia. The patient was found to be seropositive for autoantibody to the alpha-3 subunit of the neuronal nAChR. In contrast to adults with this antibody, he did not have any clinical signs of dysautonomia, and an extensive workup for malignancies was negative.

2. Case report

A previously healthy, 5.5-year-old boy from Saudi Arabia presented to the Kennedy Krieger Institute (KKI) pediatric neurology clinic with sub-acute changes in behavior and personality. Prior to the onset of these symptoms his parents described him as an average student who could talk in full sentences and had good creative play and age appropriate social interactions. His early development had been normal and he attended a private elementary school in which he regularly participated in competitive oral competitions with other students. Teachers reported gradual deterioration in his performance in these competitions over approximately 3 mo, as well as abnormal behaviors in the form of decreased social interaction, isolative behavior, self-talking, hyperactivity, and inappropriate laughter. His parents also reported motor tics and repetitive motor mannerisms like pacing and humming to himself. His play skills also decreased and it was difficult for him to pay attention to academics or to engage in social interactions with peers. The child also reported two episodes of visual hallucinations. He demonstrated behaviors of repeated hand washing and frequent urination. He also exhibited episodes of anger during which he screamed uncontrollably. He also had difficulty with sleep initiation and maintenance resulting in decreased sleep duration of 3–4 h nightly. An electroencephalography (EEG) and magnetic resonance imaging scan (MRI) of the brain as well as basic hematological and metabolic studies (24 h urine collection for copper and lead, thyroid function test and genetic tests including chromosome SNP array, fragile X at the King Faisal specialist hospital and research center in Riyadh, Saudi Arabia) were reported as normal.

Past medical history revealed that he was born at full term by repeat cesarean section following an uncomplicated pregnancy. He achieved normal developmental milestones except for a mild speech delay. He had no previous medical problems. At 4 yr of age his family reported that he developed intermittent fever for the duration of 10 mo attributed to minor illnesses for which he was given multiple courses of antibiotics. Approximately 6 mo prior to his initial presentation to KKI, he developed swelling in the left knee with elevated erythrocyte sedimentation rate at 53 mm/h, which resolved spontaneously. Diagnostic workup at that time was negative for rheumatic fever or other potential infectious or inflammatory disorders.

On physical examination at the neurology clinic at KKI, his weight was 20.4 kg (56th percentile), height was 117.5 cm (46th percentile) and head circumference was 53.5 cm (95th percentile). His vital signs showed a heart rate of 140/min, blood pressure of 112/70 mmHg, respiratory rate of 22/min and temperature of 36.4 ℃. General physical examination as well as detailed neurological examination were normal except for his mental status. He was noted to be hyperactive and difficult to engage in verbal tasks but performed within age range for non-verbal tasks. He was noted to follow simple one-step commands without gestures. He had multiple word approximations and spoke in single words sparingly. He was also noted to smile to himself and have episodes of unprovoked laughter intermittently during the exam. A speech-language evaluation revealed that he had a mixed receptive-expressive-pragmatic language disorder. He was unwilling to cooperate with much of his neuropsychological evaluation. However, the testing that he did complete showed that he had variable cognitive performance with deficits in expressive and complex verbal abilities in contrast to intact nonverbal and fine motor functioning. Although a verbal intelligence quotient could not be determined, his performance and processing speed scores on the Wechsler preschool and primary score of intelligence were within the normal range. Executive functioning was also rated on the behavior-rating inventory of executive function as normal. Pre-academic were in the average or low-average range. He demonstrated several signs of attention deficit/hyperactivity disorder but did not meet full criteria for this disorder.

2.1. Neurodiagnostic laboratory investigation

Extensive neurodiagnostic evaluation was performed at KKI. Brain MRI showed no intra-axial abnormalities. A prolonged EEG revealed focal slow activity in the right parietal occipital region. Screening blood workup was normal including a complete blood count, liver function tests, kidney function, lipids, cholesterol, vitamin D, plasma amino acids, plasma lactate and pyruvate, and serum tricarboxylic acid cycle intermediates, and co-enzyme Q10 levels. Levels of thyroid T3 and T4 as well as thyroid stimulating hormone were normal and ferritin for carbohydrate deficient glycoprotein disorders was also normal. Blood levels of C-reactive protein and erythrocyte sedimentation rate were normal. A gene array panel for mitochondrial disorders did not reveal any abnormality. Urine for organic acids was borderline positive for ethylmalonate, which was judged not to be clinically significant. Blood tests for lead, zinc, mercury, copper and ceruloplasmin showed no abnormalities. Cerebrospinal fluid (CSF) testing including protein, glucose, cell count, IgG and IgG index, and testing for herpes virus, West Nile virus and enteroviruses by polymerase chain reactions were also negative. CSF flow cytometry was negative for neoplastic cells. CSF neurotransmitter levels were normal. Two separate screening tests for quantitative serum paraneoplastic antibodies (Mayo clinic laboratories and Athena) were positive for autoantibodies against the alpha-3 subunit of the nAChR. The Mayo serum paraneoplastic panel was positive for neuronal ganglionic AChR antibody = 0.4 pmoles/L (normal < 0.02 pmoles/L).

Those panels included a wide spectrum of antibodies associated with paraneoplastic disorders: anti-N-methyl-D-aspartate, anti-voltage gated potassium channels and other antibodies known to be associated with encephalopathic and neurological manifestations. A comprehensive workup for occult neoplasm that included ultrasonographic examination of the scrotum and computerized tomography (CT) of the chest, abdomen and pelvis revealed no significant abnormality. Fluorodeoxiglucose (FDG)-positron emission tomography (PET) demonstrated no abnormalities suspicious for malignancy.

The clinical presentation and subsequent positive serology results were consistent with the clinical impression that this child had an immune-mediated cause of encephalopathy and a diagnosis of autoimmune encephalitis due to autoantibodies against the alpha-3 subunit of the nAChR was made. Therefore he was treated with five courses of plasmapheresis with albumin. After this treatment the child showed immediate improvement in his behavior and he became less agitated, established better eye contact and had improved attention, improved articulation and decreased inappropriate laughter. He was discharged to home to Saudi Arabia and maintained on monthly intravenous immunoglobulin (IVIg) treatment.

At approximately 5 mo after discharge, he was evaluated by one of us (Dr. Michael V. Johnston) in Saudi Arabia while he received an infusion of IVIg at King Faisal specialist hospital and research center in Riyadh. His parents were very pleased with his progress and reported that he was back in school doing

well in regular classes. Mother was questioned about signs of hyperactivity using the DePaul attention deficit/hyperactivity disorder rating scale IV, which she had filled in during his earlier evaluation before treatment. During the first pre-treatment evaluation, she had scored him as having 13 of 18 items on the rating scale "sometimes" but on the follow-up evaluation she rated him as having all 18 behaviors "never or rarely." He was quite calm receiving his IVIg while watching a video, in marked contrast to his agitation during his earlier treatment. Parents provided an audio in which he was repeating English words in speech therapy and his pronunciation was appropriate. Parents reported he was not talking to himself or laughing inappropriately, behaving aggressively, or having tics, and he was more socially interactive. One area that was still a problem was falling asleep at night although this too was improving.

3. Discussion

This case report describes a 5.5-year-old boy who presented with a sub-acute encephalopathic syndrome characterized by behavior and personality changes and a 3 mo gradual developmental regression with autistic features of social isolation, repetitive behaviors, and behavioral changes. His clinical presentation prompted an extensive workup for encephalopathies such as mitochondrial disorders, metabolic disorders, autoimmune disorders, and autism. Since he was developmentally normal prior to the onset of this subacute presentation, it is highly unlikely that the developmental regression was secondary to any of the pathologies associated with autism. Mitochondrial panel of tests, urine organic acid tests and blood tests for tricarboxylic acid cycle intermediates, amino acids, ammonia, lactate, pyruvate and anti-nuclear antibody were unremarkable and thus mitochondrial and metabolic causes of the developmental regression were ruled out. The patient was found to be seropositive for autoantibodies against the alpha-3 subunit of the nAChR. This autoantibody test is a part of paraneoplastic autoantibody evaluation.

Paraneoplastic neurological disorders (PNDs) comprise various neurological clinical syndromes that occur in association with occult cancer but are not due to its local effects or metastases. They may be detected in approximately 1% of adult cancer patients [9, 10]. The most commonly associated tumors with PNDs are small cell lung cancer, gynecological neoplasms and lymphoma while in children neuroblastoma is often described [11,12]. Certain neurological clinical syndromes are more often associated with neoplasm, therefore, known as classical syndromes [13]. However, clinical syndromes may also occur without cancer association [14]. The autoimmune pathogenesis has been most accepted due to the presence of specific anti-neuronal antibodies in the sera of the patients with PNDs. The expression of neuronal protein by a tumor activates the immune response which is ultimately responsible for the neurological disorder [15]. T-cell-mediated autoimmunity has also been found to contribute in the pathogenesis of PNDs . The patient in the case discussed above underwent extensive oncological evaluation because he was seropositive for autoantibodies against the alpha-3 subunit of the neuronal nAChR. Tumor screening was negative including normal full body CT, MRI of the brain and full body PET using FDG.

Earlier studies in adults have emphasized the association of alpha-3 neuronal nAChR autoantibody with idiopathic or paraneoplastic pan-dysautonomia [4–6] and cancers restricted to thymoma and small cell lung cancer. Earlier reports have [4,5,7,8] discussed the varied neurological associations in 155 adult patients seropositive for alpha-3 neuronal nAChR autoantibody. Out of these 33 (21%) had the autonomic peripheral nerve involvement (presenting as dysautonomia including gastrointestinal dysmotility, orthostatism, anhydrosis, sicca syndrome); 44 (28%) had somatic nerve involvement (presenting as sensorimotor poly-neuropathy, small fiber sensory neuropathy, polyradiculopathy, cranial neuropathy, sensory ganglionopathy, multifocal motor neuropathy) and four (2.5%) had neuromuscular junction involvement (presenting as myasthenia gravis). Twenty-six (17%) out of 155 patients had central nervous system involvement which included neuropsychiatric disorders, extrapyramidal disorders, demyelinating central nervous system disorders and stiff-man syndrome. Forty-eight (31%) patients had either a non-autoimmune neurological disorder or no neurological disorder at all. Out of the 155 seropositive patients 78 (50%) had had oncological evaluation and 30 (38%) were confirmed to have cancer. Adenocarcinoma was most common (43%), followed by lymphoid neoplasms (17%), renal cell carcinoma (6%) and 34% had other neoplasms. Therefore this autoantibody is associated with more diverse oncological and neurological

associations than were originally described.

With increased titers of anti-neuronal antibody, it is highly probable that the neurological manifestation in our patient was paraneoplastic. In 60–70% of the cases, tumors may arise several years after the neurological manifestation. Detection of a tumor early may facilitate curative treatment. Therefore, a thorough oncological evaluation should be performed in such patients. CT or MRI scan of thoracic, abdominal and pelvic regions can detect most tumors. However, if no tumor is found using a CT or MRI scan, a whole body PET with FDG should be performed [16,17]. In the treatment of PNDs, the first approach should include cancer therapy (surgery, radiotherapy, chemotherapy). However, in many instances no evidence of cancer is found. Thus, a second therapeutic approach can be directed at the immune response (immune suppression, plasmapheresis, IVIg). Immunosuppressive treatment should be started as early as possible so as to prevent T-cell mediated irreversible damage in the nervous system [18]. A third therapeutic approach may be symptomatic management, focused on disabling symptoms such as psychosis, dysautonomia or seizures [19]. Since the oncological survey was negative in our patient, we opted for an immunomodulatory therapy to which he responded well. On literature review of similar cases in adults, the outcome was noted to be better for patients treated with plasmapheresis when compared to steroids; hence after discussion with our resident neuroimmunologist (Dr. Carlos Pardo), the clinical team opted for plasmapheresis as the treatment of choice over high dose steroids. Currently the patient is ongoing maintenance immunomodulation therapy with monthly IVIg. The treatment plan is to continue the monthly IVIg for at least 6 mo and then gradually either decrease the monthly dose or increase time between infusions from monthly to every 6 wk and thus slowly taper him off the IVIg. Once he is completely off the IVIg, we will repeat the PND panel to monitor for post-treatment antibody levels. And at that time again repeat the neuroimaging and whole body PET and CT scans to monitor for any occult neoplasms.

Cases of PNDs as well as those with a similar encephalopathic presentation but without any detectable neoplasm have been described previously in the adult literature. This case described above is the first report of a pediatric patient seropositive for neuronal ganglionic nAChR autoantibody presenting with subacute development of neuropsychiatric symptoms due to central nervous system involvement, apparently without an associated occult neoplasm. We would like to illustrate the point that it is important to perform a screening for paraneoplastic disorders in previously healthy children presenting with acute or sub-acute developmental regression in which the workup for infectious, inflammatory, metabolic or mitochondrial etiology is negative.

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