moleculera labs

Cunningham Panel™ Testing Results

Patient Name: Last Name, First Name
Patient DOB: MM/DD/YYYY
Patient ID Number: C000-001-XX
Date of Test Report: 09/17/2015

PATIENT REPORT

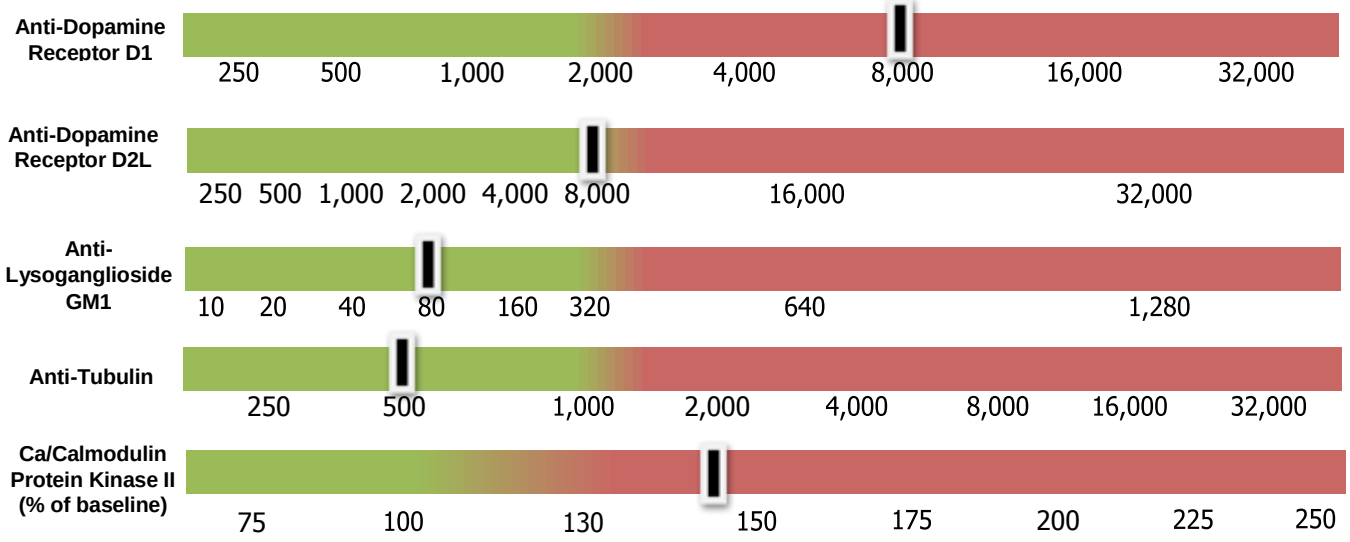
Submitting Prescriber: Doctor Name, MD
Date of Collection: MM/DD/YYYY
Date of Receipt: MM/DD/YYYY

LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	**1:8,000**	**1:8,000**	**1:80**	**1:500**	**145**
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53-130
Normal Mean	1,056	6,000	147	609	95
INTERPRETATION*	**ELEVATED**	**BORDERLINE**	**NORMAL**	**NORMAL**	**ELEVATED**

***Report Guidance:** If any one (1) or more of these five (5) assay values is elevated, it may indicate a clinically significant autoimmune neurological condition. This is a condition in which the patient's autoantibodies cross-react and are directed against selected neuronal targets which are involved in normal neuropsychiatric and/or motor functions. It is important to note that the degree of elevation in assay values may not necessarily correlate with degree of symptom severity, as any value above normal ranges may correlate with symptomatology.

LABORATORY TEST RESULTS



The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) directed against: Dopamine D1 Receptor (DRD1), Dopamine D2L Receptor (DRD2L), Lysoganglioside-GM1 (LYSO-GM1) and Tubulin (TUB). ELISA results are determined by measuring the colorimetric intensity at a specific wavelength which is directly proportional to the amount of antibody in the sample. The fifth assay of this panel measures the specific activity of calcium/calmodulin-dependent protein kinase II (CaM KII) induced by the patient serum in cultured human neuronal cell lines compared to controls. This panel measures the level of these antibodies, and the ability of the patient's sera to stimulate CaM KII at a single point in time. Results may vary depending on the patient's condition and status, whether they are on immunosuppressive agents, corticosteroids or other immune modulatory therapy, and the length of time post treatment.

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PANDAS and PANS are clinical diagnoses based upon defined clinical characteristics. The results from the Cunningham Panel are provided as an aid to the physician in their diagnosis of PANDAS or PANS. This test panel is used for clinical purposes and should not be regarded as investigational or for research. This test has been developed and its performance characteristics determined by Moleculera Labs, Inc. It has not been cleared or approved by the U. S. Food and Drug Administration. Moleculera Labs, Inc. and the Cunningham Panel are regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform diagnostic clinical testing. This test is physician ordered and is meant to be used in conjunction with a complete medical exam. ***There may be additional risk and diagnostic factors not measured by this test.*** The Cunningham Panel and Moleculera are trademarks of Moleculera Labs, Inc. This test has patents pending in the U.S. and internationally. For more information please call (405) 239-5250 or e-mail us at customerservice@moleculera.com. CLIA Number: 37D2052130; COLA ID: 24220. Kenneth Mueller, PhD, HCLD/CC (ABB), FNACB, Clinical Laboratory Director (975 NE 10th Street, Room 215, Oklahoma City, OK 73104). CLIA Number: 37D2082408; COLA ID: 25744. Joseph Quashnock, PhD, HCLD/CC (ABB), FACB, Clinical Laboratory Director (755 Research Parkway, Suite 448, Oklahoma City, OK 73104).

Reviewing Results

Anti-Neuronal Antibody Results

This report lists four anti-neuronal antibody test results which measure circulating levels of autoantibodies directed against specific neuronal antigens in the patient at the time the specimen was collected. These antigens include: Dopamine D_1 Receptor (DRD1), Dopamine D_{2L} Receptor (DRD2L), Lysoganglioside-GM1 (LYSO-GM1) and Tubulin (TUB). These laboratory results are expressed as the "titer" or final dilution at which an endpoint reaction was observed on an Enzyme-Linked ImmunoSorbent Assay format (ELISA). Eg. If the patient's titer is 1,000 that means that the patent's sample required a 1,000-fold dilution to reach a set endpoint for the particular anti-neuronal antibody measured. Each assay was performed in duplicate against each of the four (4) neuronal antigens. Directly below the patient's titer are the "normal ranges" in normal children without infection measured against each respective antigen. It is possible that "normal ranges" for adults may differ from normal ranges in children.

CaM Kinase II Activation

This laboratory value is a numeric score that reflects the percent of baseline CaM Kinase activity in a human neuronal cell line. Eg. If the patients score was 170, it means that the patient's sample stimulated CaM Kinase activity in a human neuronal cell line, at 170% over baseline activity. Directly below the laboratory value is the "normal range" value measured in normal children without infection. It is possible that "normal ranges" for adults may differ from normal ranges in children. CaM Kinase is an enzyme present in neuronal cells and is part of the activation pathway for the production of dopamine.

Other Factors

The laboratory results reflect the status of the patient at time their specimen was drawn. Certain treatments are believed to impact the results of these tests. These include: systemic steroids, IVIG and Plasma Exchange. For this reason we generally recommend that the patient wait to be tested approximately 6-8 weeks or longer after these treatments. However, it is possible that these treatments may not affect the results to the degree that an autoimmune condition would not be identifiable. Therefore, the timing of testing is best determined by the ordering physician and their assessment of the condition and status of the patient.

What is PANDAS?

PANDAS is an acronym for "Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection." This condition was first described by Dr. Susan Swedo at the National Institutes of Mental Health in 1998[1]. PANDAS has been described as presenting with an acute onset of obsessive-compulsive disorder (OCD) and/or motor tics in children with a recent streptococcal infection[1,2]. The clinical existence of PANDAS was published in a 2002 study[2] showing evidence of a temporal association

of group A streptococcal tonsillopharyngitis and abrupt onset of OCD in 12 children. In all 12 children, treatment with antibiotics resulted in rapid reduction in OCD symptoms.

PANDAS is classified as one of the conditions on the spectrum of neuropsychiatric disorders caused by group A streptococcal infection and autoimmunity. The first condition described in this spectrum was Sydenham's Chorea[3] which demonstrates considerable clinical and immunological overlap with the presentation and mechanism of action of PANDAS. Studies from the NIH, as early as 1958, reported high rates of OCD behaviors in children with Sydenham's Chorea[4-6]. Neuropsychiatric symptoms predate the choreiform movements in this disorder. In addition, a subgroup of children with the onset of OCD and/or Tics was associated with a recent group A streptococcal infection and did not meet criteria for Sydenham's chorea was identified[7]. This subgroup was subsequently identified as PANDAS[8].

The immunological mechanism of Sydenham's Chorea has been identified as an antibody produced in response to a group A streptococcal infection, which cross-reacts with extra- and intracellular neuronal targets in the basal ganglia[9,10]. Specifically, anti-neuronal IgG antibodies, found in sera of patients with Sydenham's Chorea, target basal ganglia resulting in the disease state[10].
PANDAS appear to have a similar etiopathogenesis as Sydenham's Chorea[11]. The clinical symptoms of OCD and motor tics are reported to follow a child's contraction of a group A beta-hemolytic streptococcal infection, most commonly tonsillopharyngitis. The clinical characteristics of PANDAS are 1) prepubertal onset; 2) appearance of OCD symptoms and/or motor tics; 3) abrupt onset of OCD behaviors or motor tics and episodic course correlating with group A streptococcal infections[1,12,13]. PANDAS has also been reported in children with an existing tic disorder or Tourette's syndrome[14-17]. In this scenario, the baseline frequency of the child's tics may markedly increase when the child has a strep infection and return to baseline rates after antibiotic treatment[18,19].
The neuroanatomical correlates of PANDAS, as with tics, OCD and Sydenham's Chorea, are the basal ganglia and dopamine receptors[8]. Children with PANDAS have been found to have significantly larger basal ganglia structures on MRI than healthy age-matched controls[20]. There is evidence that both the basal ganglia and dopamine receptors are targeted by Group A streptococcal infection-associated autoantibodies in this condition[21-25]. Autoimmune reactions in Group A streptococcal infections are well known to occur in post-streptococcal glomerulonephritis and rheumatic fever[26].

Studies have shown children that meet the clinical criteria for PANDAS have higher levels or circulating antibodies targeting the caudate and putamen neuronal surface antigens in the midbrain compared to children with Tourette's syndrome or other tic disorders[22,23]. Specific antibodies against neuronal surface glycolytic enzymes, lysoganglioside and N-acetyl-β-D-glucosamine, are found to be in higher concentrations and more active in children with tics compared to those children with only Group A streptococcal pharyngitis and without tics[27,28]. Current findings support the hypothesis that there is an abnormal immunological response in those with the clinical symptoms of PANDAS[11,21]. These findings will allow a more specific diagnostic laboratory tool that will allow a more precise and rapid confirmation of PANDAS. Identification of autoantibodies directed against specific neurologic receptors may assist the clinician in making an accurate and timely diagnosis of PANDAS potentially allowing for effective treatment strategies to be implemented.

What is CANS and PANS?

Childhood Acute Neuropsychiatric Symptoms (CANS)[29] and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)[30] are proposed as a new, broader classification that would expand both the etiological infectious agents and the clinical manifestations, to the current description of PANDAS[30]. This is an important development since there are reported cases of patients fulfilling the clinical criteria of PANDAS but laboratory studies are negative for a recent group A streptococcal infection. Published reports have postulated that stress[31] as well as other types of infections can result in neuropsychiatric conditions, which include Borrelia burgdorferi (Lyme disease), Mycoplasma pneumonia, herpes simplex, common cold and varicella viruses[32-36].

The classification of CANS is proposed to include individuals that present following an infectious illness, with an acute and dramatic onset of neuropsychiatric symptoms not limited to OCD and tics[29]. Identification of a specific infectious agent may be difficult in certain cases, but the immune response against the infection is proposed to be the cause of the symptoms[10,11]. It has been proposed that CANS may occur at any age and does not result in recurrent episodes of symptom exacerbations[29].

The definition of neuropsychiatric symptoms is broad, but current consensus is that many of the symptoms previously reported in PANDAS be included[29]. CANS would include the acute, post-infectious onset of OCD, anxiety, anorexia, conduct disorders, attentional and concentration deficits, depression, fine motor deficits, emotional lability, hyperactivity, irritability and sleep disorders. These symptoms may be isolated or in combination and not be the result of another medical condition.

Is There Treatment for PANDAS and PANS?

Reported treatments include eradicating the underlying infectious agent and reducing the immunological response that has been reported to cause the neuropsychiatric symptoms. The literature indicates that there are several proven effective PANDAS treatments that result in prompt resolution of both OCD and motor tics. Antibiotic treatment addresses the underlying group A streptococcal, or other bacterial infections and therefore reduce the immune system responses. Additional treatment methods specifically target the autoantibodies that cause PANDAS. Both IVIG and plasma exchange have been proven to be effective in significantly reducing symptoms in randomized control studies[37].

The effectiveness in treating group A streptococcal infections, with subsequent resolution of PANDAS symptoms, has been shown in several studies. One study reports confirmed resolution of OCD symptoms and tics following antibiotic treatment and subsequent negative throat cultures in patients the group-A streptococcal tonsillopharyngitis[2]. There are some children that are defined as group A streptococcal carriers and are asymptomatic, without signs of tonsillopharyngitis. These individuals may continue to generate the streptococcal related antibodies and harbor organisms in their nasopharynx[38-40].

With current opinion that post-infectious autoimmunity is the cause of neuropsychiatric symptoms, then it was hypothesized that plasma exchange and intravenous immunoglobulin (IVIG) treatment may be an effective treatment. There are published reports of successful resolution of symptoms associated with PANDAS treatment with plasma exchange and IVIG treatment[37,41].
There is one published case series of 4 adult patients presenting with an acute onset of OCD and tics following a documented group A streptococcal infection[42]. These patients would fulfill the criteria for CANS and were treated with plasmapheresis. In a separate placebo controlled study, adults with non-specific tics disorders did not show statistical improvement in symptoms with IVIG treatment[43].

It is reported that repeated group A streptococcal infections result in recurrent, episodic exacerbations of clinical symptoms[8] in PANDAS. During the affected period, the children may manifest concurrent new onset fine motor deterioration and personality/behavioral changes including abnormal movements of the head, neck and extremities. A range of personality and behavioral changes including hyperactivity, irritability, attentional problems and oppositional behaviors are also associated with the onset of PANDAS in children[13].

Although there are reports of successful resolution of PANDAS symptoms with antibiotics, plasma exchange and IVIG therapy, there are still concerns regarding the proper identification of patients that fulfill criteria for PANDAS and are candidates for therapy[29,44]. Early diagnosis and prompt treatment may prevent the significant social, emotional and educational toll that OCD and tics have on affected children and their families. Unnecessary stress and anxiety will be prevented with appropriate diagnosis and treatment of PANDAS.

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