

The First Pilot Epigenetic Type Improvement of Neuropsychiatric Symptoms in a Polymorphic Dopamine D2 (-DRD2/ANKK (Taq1A)), OPRM1 (A/G), DRD3 (C/T), and MAOA (4R) Compromised Preadolescence Male with Putative PANDAS/CANS: Positive Clinical Outcome with Precision-Guided DNA Testing and Pro-Dopamine Regulation (KB220) and Antibacterial Therapies

Kenneth Blum^{1,2,3,4,5,6,7,8,9,10,11,12*}, Igor Elman¹³, David Han¹⁴, Colin Hanna¹⁵, David Baron¹, Ashim Gupta¹⁶, Shan Kazmi¹, Jag Khalsa¹⁷, Debasis Bagchi¹⁸, Thomas McLaughlin⁶, Rajendra D. Badgaiyan¹⁹, Edward J. Modestino²⁰, Drew Edwards²¹, Catherine A. Dennen²², Eric R. Braverman⁶, Abdalla Bowirrat⁷, Keerthy Sunder^{8,23}, Kevin Murphy⁹, Nicole Jafari^{10,24}, Foojan Zeine^{11,25}, Paul R. Carney²⁶, Mark S. Gold²⁷, Kai-Uwe Lewandowski¹², Alireza Sharafshah²⁸, Aryeh R. Pollack⁶, Panayotis K. Thanos^{15*}

¹Division of Addiction Research & Education, Center for Sports and Mental Health, Western University of Health Sciences, Pomona, CA, USA

²Department of Psychiatry, Boonshoft School of Medicine, Wright State University and Dayton VA Medical Centre, Dayton, OH, USA

³Division of Nutrigenomics, Victory Nutrition International, Lederoch, PA, USA

⁴Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary

⁵Department of Psychiatry, School of Medicine, University of Vermont, Burlington, VT, USA

⁶The Kenneth Blum Behavioral & Neurogenetic Institute, LLC., Austin, TX, USA

⁷Department of Molecular Biology, Adelson School of Medicine, Ariel University, Ariel, Israel

⁸Division of Neuromodulation Research, Karma Doctors & Karma TMS, Palm Springs, CA, USA

⁹Division of Personalized Interventions, Peak Logic, Del Mar, CA, USA

¹⁰Division of Personalized Medicine, Cross-Cultural Research & Educational Institute, San Clemente, CA, USA

¹¹Awareness Integration Institute, San Clemente, CA, USA

¹²Division of Personalized Pain Therapy, Center for Advanced Spine Care of Southern Arizona, Tucson, AZ, USA

¹³Department of Psychiatry, Harvard School of Medicine, Cambridge, MA, USA

¹⁴Department of Management Science and Statistics, University of Texas, San Antonio, TX, USA

¹⁵Behavioral Neuropharmacology and Neuroimaging Laboratory, Clinical Research Institute on Addictions, Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA

¹⁶Future Biologics, Lawrenceville, GA, USA

¹⁷Department of Microbiology, Immunology, & Tropic Diseases, School of Medicine, Georgetown University, Washington DC, USA

¹⁸Department of Pharmaceutical Sciences, College of Pharmacy, Texas Southern University, Houston, TX, USA

¹⁹Department of Psychiatry, School of Medicine, Case Western University, Cleveland, OH, USA

²⁰Brain and Behavior Laboratory, Curry College, Milton, MA, USA

²¹The Neurogenesis Project, Jacksonville, FL, USA

²²Department of Family Medicine, Jefferson Health Northeast, Philadelphia, PA, USA

²³Department of Psychiatry, UC Riverside School of Medicine, University California, Riverside, CA, USA

²⁴Department of Human Development, California State University at Long Beach, Long Beach, CA, USA

²⁵Department of Health Science, California State University at Long Beach, Long Beach, CA, USA

²⁶Division Pediatric Neurology, School of Medicine, University of Missouri, Columbia, MO, USA

²⁷Department of Psychiatry, School of Medicine, Washington University, St. Louis, MO, USA

²⁸Cellular and Molecular Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

Email: *drd2gene@gmail.com, *thanos@buffalo.edu

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Abstract

Pediatric autoimmune neuropsychiatric disorders associated with or without streptococcal and other bacterial infections (PANDAS/CANS) are emerging as a featured pediatric disorder. Although there is some controversy regarding treatment approaches, especially related to the behavioral sequelae, we have hypothesized in other published work that it is characterized by the rapid onset of Reward Deficiency Syndrome (RDS) in children. We propose utilizing a multi-systems biological approach involving the coupling of genetic addiction risk testing and pro-dopamine regulation (KB220/POLYGEN®) to help induce “dopamine homeostasis” in patients with PANDAS, especially those with known DNA-induced hypodopaminergia. This case study examines a 12-year-old Caucasian male with no prior psychiatric issues who presented with a sudden onset of severe anxiety, depression, emotional lability, and suicidal ideation. The patient underwent genotyping and the genetic addiction risk score (GARS) testing, which revealed risk polymorphisms in the dopamine D2 (-DRD2/ANKK (Taq1A), OPRM1 (A/G), DRD3 (C/T), and MAOA (4R) genes. These polymorphisms have been linked to hypodopaminergia. The patient was subsequently placed on research ID-KB220ZPBMPOLY (POLYGEN®), and albeit the possibility of bias, based upon self and parental assessment, a marked rapid improvement in psychiatric symptoms was observed. In the second phase of treatment (102 days utilizing KB220), the patient received standard antibody testing, which was positive for Lyme. Antibacterial therapy started immediately, and KB220z was discontinued to provide a wash-out period. A monotonic trend analysis was performed on each outcome measure, and a consistently decreasing trend was observed utilizing antibacterial therapy. Our recommendation, albeit only one case, is to utilize and further research a combined therapeutic approach, involving precision-guided DNA testing and pro-dopamine regulation along with antibacterial therapy, as well as glutathione to address offensive enhanced cytokines, in patients with suspected PANDAS/CANS.

Keywords

PANDAS, CANS, Genetic Addiction Risk Testing (GARS), Pro-Dopamine

1. Introduction

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, Lyme, and other bacterial infections (PANDAS) are emerging as a featured pediatric disorder whereby a subset of children, especially in preadolescence, have a rapid onset of Reward Deficiency Syndrome (RDS) [1] [2], which includes obsessive-compulsive disorder (OCD), anxiety, depression, avoidant behaviors, and/or tic disorders. Additionally, learning regression, deterioration in handwriting, night-time fears, emotional lability, and separation anxiety have been documented in affected children. Dopamine function appears to play a significant role in RDS. However, dopamine is just one of several critical neurotransmitters in the mesolimbic/prefrontal cortex and brainstem, each playing an important role in managing behavior [3]. In unpublished work from Dr. Chris Turnpaugh's, Health & Wellness Center (Mechanicsburg, PA) and others, certain foods like mint could affect both d1 and d2 receptor integrity.

These RDS and other mood behaviors may arise from group A beta-hemolytic streptococcal (GABHS) infections [1] [2]. Lyme and *Borrelia*, as well as other GABHS infections, can induce an autoimmune reaction and concomitant antibodies that interfere with normal brain function, specifically targeting mesolimbic dopaminergic loci [2]. Previously, our group suggested that Lyme disease's principal vector in the United States is *Ixodes scapularis* (deer or black-legged ticks) and that those infected may present depression and anxiety, possibly due to hypodopaminergia [4]. Transcripts coding for two putative cytosolic sulfotransferases were also identified in this study, which demonstrated that these ticks recognized phenolic monoamines as their substrates. Specifically, sulfotransferase activity was found in later recombinant proteins against the neurotransmitters dopamine and octopamine. Furthermore, it was demonstrated in the salivary glands of Ixodid ticks that the activation of *Ixosc Sult 1* and *Sult 2* may cause the inactivation of the salivation signal through the sulfonation of either octopamine or dopamine. This, by itself, can cause RDS behaviors.

PANDAS is a subset of pediatric acute neuropsychiatric symptom (PANS). The current diagnosis of PANDAS and the hypothesized infection pathology is controversial [5]-[10]. Singer [10] [11] considered PANS to have numerous unknown causes, one of which might include hypodopaminergia [11]. The treatment of PANDAS remains disputed, especially since there have been limited efficacy studies to date [12]. Previously, we proposed an innovative potential treatment for PANDAS based on previous clinical trials using a pro-dopamine regulator known as KB220 variants. Our ongoing research suggests that achieving "dopamine homeostasis" by precision-guided DNA testing and pro-dopamine modulation could result in improved therapeutic outcomes [12].

It is indeed well known that PANDAS can result in a neuroinflammatory response influencing the dysfunction of TH1 and TH2 lymphocytes T cells. Importantly, these T cells are key mediators of adaptive immunity. Briefly, the specificity of the T cells response is related to the antigen-specific receptors they express, the **TCRs** (T Cell Receptor). It should be pointed out that, like immunoglobulins expressed by B cells, TCRs are somatically generated, and their diversity is obtained by random rearrangements of their gene segments. Moreover, T cells only recognize antigens once these have been processed into peptides and exposed onto the surface of the target cell, in an antigen presentation structure known as the **Major Histocompatibility Complex** (MHC). In fact, it is well known that the MHC-antigen complex binding to the TCR is the first mandatory step for T cell activation. Furthermore, the crucial role of Th1 and Th2 in the immune response, the mechanisms leading to the priming of naïve CD4+ T cells into Th1 or Th2, it is clear that the cytokine microenvironment is fundamental in the process, as well as the strength of the stimulatory signals from the APC (*i.e.*, the affinity of TCR for the peptide ligand). Understanding this basic information provides the rationale whereby PANDAS and associated infection induce a disruption of this important physiological elemental construct [13]. While our study did not address this important issue, we are compelled to at least realize that in conjunction with our approach as described herein to offer potential assistance linked to the RDS type of behaviors, neuroinflammation must also be treated. For example, clinicians have employed a number of natural ingredients such as glutathione, perilla, cumin, luteolin, fisetin, and others known to reduce neuroinflammatory processes [14].

The present case report supports our hypothesis, serving as a starting rationale for conducting larger randomized-control studies on this topic.

2. Materials and Methods

Sequence of Events: The subject was a 12-year-old Caucasian male with no previous psychiatric episodes. On 7/20/2020, the patient tested for Genetic Addiction Risk Severity (GARS). GARS was initially conducted because MP (the mother), taking note of many unwanted behaviors (including suicidal ideation), knew of KB's work in the area of RDS. The GARS results identified DNA polymorphisms associated with low dopamine function. While this test has been validated to capture polymorphisms of reward genes (see 17), the test has not as yet received approval from the FDA. The KB220 product, with customized ingredients matching the measured polymorphisms reflected in GARS results, was subsequently administered to induce "dopamine homeostasis" (KB220ZPBM-POLY [POLYGEN®]). The patient started the KB220z within 30 days of testing (8/18/2020).

A physician suspected PANDAS/CANS following a visit on 2/18/2021. The pediatrician confirmed the diagnosis with antibody titers for Strep, Lyme, and Borrelia (**Table 1, Figure 1 & Figure S1**). Prior to this, neither MP nor KB considered PANDAS to be the reason for the rapid onset of RDS behaviors. The pro-dopamine

regulator was administered for *seven months* prior to involving a pediatric PANDAS/CANS specialist. The patient was subsequently (2/19/21) placed on anti-bacterial medication, stopping the pro-dopamine regulator to ensure a reasonable wash-out period. This was done because the attending physician wanted to see the results of the antibacterial treatment alone. This sequence of events, which is unorthodox in terms of traditional patient care, is summarized in **Figure 2**.

Table 1. Pertinent blood testing/antibody titer results.

DNASE B ANTIBODY	622 (U/mL)	<376 Negative	
		Deficiency: <20 ng/mL	
VITAMIN D, 25-OH, TOTAL, IA	25 (ng/mL)	Insufficiency: 20 - 29 ng/mL	
		Optimal: > or = 30 ng/mL	
MYCOPLASMA PNEUMONIAE ANTIBODIES (IGG, IGM)			
MYCOPLASMA PNEUMONIAE ANTIBODY (IGG)	1.71	≤0.90	Negative
		0.91 - 1.09	Equivocal
		≥1.10	Positive
MYCOPLASMA PNEUMONIAE ANTIBODY (IGM)	671 (U/mL)	<770 U/ml	Negative
		770 - 950 U/mL	Low positive
		>950 U/mL	Positive
EPSTEIN BARR VIRUS ANTIBODY PANEL			
EBV VIRAL CAPSID AG (VCA)	<36.00 (U/mL)	<36.00	Negative
		36.00 - 43.99	Equivocal
		>43.99	Positive
EBV VIRAL CAPSID AG (VCA)	220.00 (U/mL)	<18.00	Negative
		18.00 - 21.99	Equivocal
		>21.99	Positive
EBV NUCLEAR AG (EBNA)	>600.00 (U/mL)	<18.00	Negative
		18.00 - 21.99	Equivocal
		>21.99	Positive
HERPESVIRUS 6 ANTIBODIES (IGG, IGM)			
HERPESVIRUS 6 AB (IGG)	1:10 (titer)	<1:10 Negative	
HERPESVIRUS 6 AB (IGM)	<1:20 (titer)	<1:20 Negative	

Genetic Testing: In this case, study protocols were reviewed and approved by the PATH Foundation (NY) Institutional Review Boards (IRB). The genotyping data complied with accepted Genetic Information Non-Discrimination Act (GINA) and Health Insurance Portability and Accountability Act (HIPAA) practices, which are mandated by law to protect patient privacy. Written and informed consent was provided and approved by the primary participants.

TEST	SPECIMEN	RESULT	REFERENCE RANGE	UNITS
Lyme Western Blot IgG	Serum			
IGX Criteria:		Positive		
CDC/NYS Criteria:		Negative		

Band (kDa)	18	23-25*	28	30	31*	34*	39	41	45	58	66	83-93*
Intensity	-	-	+	-	-	+	-	+	-	-	-	-

Band Intensity: Positive: + to +++, Indeterminate: Ind, Negative:(-)

INTERPRETATION

Positive

IGX CRITERIA

2 or more of the starred bands are present (+): 23-25*, 31*, 34*, 39*, 41*, 83-93* kDa

CDC/NYS CRITERIA

5 or more of the following bands are present(+): 18, 23-25*, 28, 30, 39*, 41*, 45, 58, 66, 83-93* kDa

Indeterminate

Only bands 31* and 41* kDa are present, test 489 is recommended for confirmation

N/A

Negative

Does not meet IGX criteria for a positive or indeterminate test result.

Does not meet CDC/NYS criteria for positive or indeterminate test result.

Limitation: Bands 31* and 34* kDa are present in Lyme vaccinated patients. Viral antibodies cross react with antigens present at band positions 31* and 83-93* kDa.

Figure 1. The results and interpretation of the patient's Lyme Western Blot IgG. Results indicated that the patient was positive for Lyme, according to the IGX criteria. For a more comprehensive list of blood/antibody testing performed, please refer to **Figure S1**.

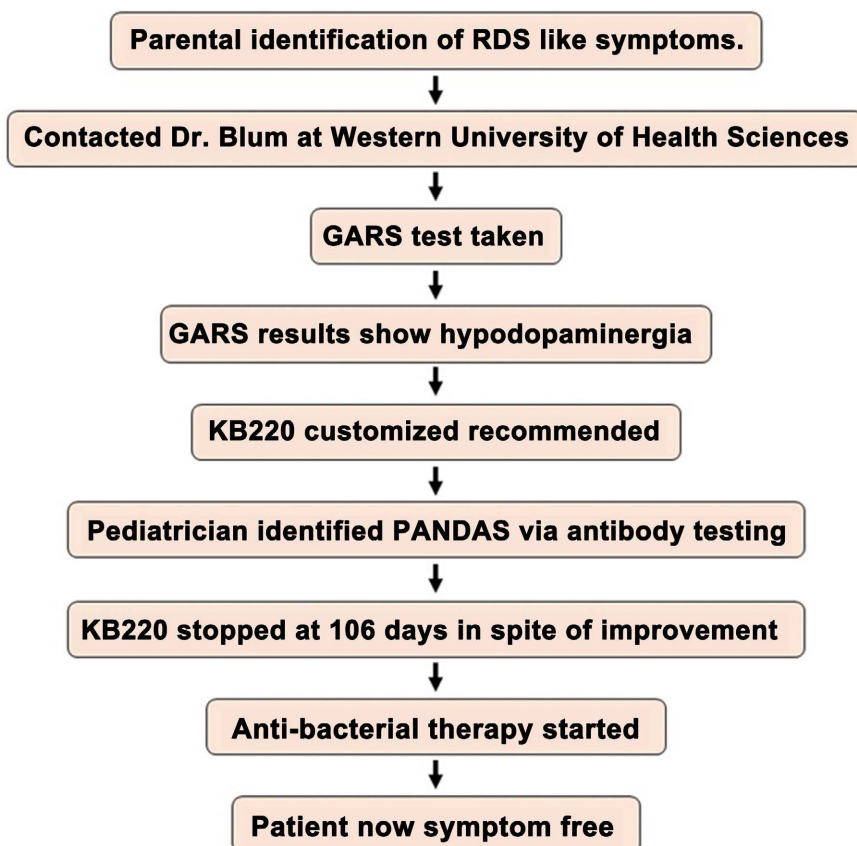


Figure 2. Flow chart summarizing the treatment events for the patient.

The biotechnical methods used to identify GARS risk alleles have been previously published in detail [15]. Cheek swabs were obtained from the patient and taken to Genus Health (San Antonio, Texas) for further processing. PCR amplification was used to isolate DNA, which was then analyzed for polymorphisms in the following genes: DRD1, DRD2, DRD3, DRD4, OPRM1, COMT, DAT1, DRD4-R, GABRB3, HTTLPR, and MAOA. An index of the genes incorporated in the GARS assay and the specific risk polymorphisms are supplied in **Tables 2(a)-(c)**.

Table 2. (a) single nucleotide polymorphisms (SNPs); (b) simple sequence of repeats (variable number tandem repeats and insertion/deletions); (c) dinucleotide repeats.

(a)			
GENE	POLYMORPHISM	VARIANT ALLELES	RISK ALLELE
Dopamine D1 Receptor DRD1	rs4532	A/G	A
Dopamine D2 Receptor DRD2	rs1800497	A/G (A1/A2)	A (A1)
Dopamine D3 Receptor DRD3	rs6280	C/T	C
Dopamine D4 Receptor DRD4	rs1800955	C/T	C
Catechol-O-Methyltransferase COMT	rs4680	A/G (Met/Val)	G (Val)
Mu-Opioid Receptor OPRM1	rs1799971	A/G (As/Asp)	G (Asp)
(b)			
GENE	POLYMORPHISM	VARIANT ALLELES	RISK ALLELE
Dopamine D4 Receptor DRD4	rs761010487	48bp repeat 2R - 11R	≥7R, long form
Dopamine Active Transporter DAT1	rs28363170	40p repeat 3R - 11R	< 9R
Monoamine Oxidase A MAOA	rs768062321	30bp repeat 2R - 5R	3.5R, 4R, 5R
Serotonin Transporter SLC6A4 (5-HTTLPR)	rs4795541, rs25531	43bp repeat, with SNP L/XL and S, G/A	S, LG
(c)			
GENE	POLYMORPHISM	VARIANT ALLELES	RISK ALLELE
GABA(A) Receptor, Alpha-3 GABRB3	rs764926719	CA dinucleotide repeat 171 - 201bp sized fragments	181

KB220Z: The neuro-nutrients classified as KB220ZPAM/PBM have been genetically formulated to provide maximum results based on GARS results (**Table 3**). The six different formulations were scientifically developed based on a person's genetic risk variants. Based on the patient's GARS results, we used KB220ZPBM-POLY (POLYGEN), a genetically based formula created to provide precision supplementation to overcome dopamine, serotonin, endorphin, and GABA deficits. These deficits are the result of multiple systems and integrative polymorphic genes affecting the Brain Reward Cascade (BRC) and causing impairments across the BRC. This leads to low dopamine function, which in turn causes reward deficiency or an overall lack of well-being [16].

Table 3. GARS repeats primer details.

PRIMER	SEQUENCE (5' to 3')	5' LABEL	REACTION (nM)
AMELO-F	CCC TGG GCT CTG TAA AGA ATA GTG	NED	150
AMELO-R	ATC AGA GCT TAA ACT GGG AAG CTG	-	
MAO-F	ACA GCC TGA CCG TGG AGA AG	NED	120
MAO-R	GAA CGG ACG CTC CAT TCG GA	-	
DAT-F	TGT GGT GTA GGG AAC GGC CTG AG	6FAM	120
DAT-R	CTT CCT GGA GGT CAC GGC TCA AGG	-	
DRD4-F	GCT CAT GCT GCT GCT CTA CTG GGC	VIC	480
DRD4-R	CTG CGG GTC TGC GGT GGA GTC TGG	-	
GABRA-F	CTC TTG TTC CTG TTG CTT TCA ATA CAC	NED	120
GABRA-R	CAC TGT GCT AGT AGA TTC AGC TC	-	
HTTLPR-F	ATG CCA GCA CCT AAC CCC TAA TGT	PET	120
HTTLPR-R	GAG GGA CTG AGC TGG ACA ACC AC	-	

Putative Diagnostic Basis of PANDAS: Throat swabs from the patient underwent a rapid antigen detection test for Group A Streptococci, Lyme, and Borrelia, performed in accordance with the manufacturer's instructions. Samples were placed into a tube with a standard reagent solution and mixed forcefully in order to extract the specimen into the suspended solution. After mixing and then subsequently letting the solution stand for two minutes, the swab was removed and discarded. The absorbent end of a test stick was then placed into the tube with the extracted specimen. Results were read after 5 minutes. The results were considered positive if a test line and control line appeared on the test stick and negative if only the control line appeared. A positive result indicated that the assay had detected Group A Streptococcus antigen within the extracted specimen. A negative result indicated that there was no Group A Streptococcus antigen within the extracted specimen.

Based on the positive diagnostic workup by the attending physician utilizing standard antibody testing, the presence of antibodies to Streptococcus, and Lyme but not Borrelia were found. The patient was placed on the following antibacterial

medications: Amoxicillin-Clavulanic acid, 875 - 125 mg (Augmentin); Sulfamethoxazole-trimethoprim 800 - 160 mg (Bactrim); Naproxen 500 mg (Naproxen); Doxycycline Hyclate, 100 mg; Cefdinir, 300 mg. (All BID, generally tolerated, some stomach issues presented).

Statistical Analysis

A monotonic trend analysis was performed on each outcome measure (in Likert scales), showing a consistently decreasing trend when compared to the baseline measurement ($p < 0.05$). The data was tabulated by the mother (MP) as self-reported by the patient (AP) and further verified by the father. Because of potential bias, all three had to agree with the data entry. The patient's tabulated behavioral response, including behavioral symptoms (pain, suicide ideation, focus, etc.) and psychiatric syndromes (agoraphobic, body-dysmorphic, etc.) have been graphed in **Figure 3(a)** (pro-dopamine regulation) and **Figure 3(b)** (antibacterial). While a psychiatrist was not involved in these entries, we feel confident that the described responses are correct.

3. Results

GARS test results revealed four heterozygous polymorphic risk alleles: DRD2/ANKK (Taq1A), OPRM1 (A/G), DRD3 (C/T), and MAOA (4R), revealing hypodopaminergia. Based on these results, the patient was immediately placed on KB220ZPBMPOLY. The patient's tabulated behavioral results are found in **Figure 3** and **Table S1**. Based on the data in **Figure 3**, all features were found to decrease over time when compared to the baseline measurements, except for pain (no change was observed). There was very rapid relief of many symptoms in the patient from day one, and that was maintained for 102 days. There was no significant trend due to this surprising rapid relief finding.

In the second (antibacterial) phase of treatment, all features decreased in scale. Suicide Ideation, OCD, and Focus were insignificant ($p > 0.14$). Depression ($p = 0.04$), Anxiety ($p = 0.04$), and Pain ($p = 0.022$) significantly decreased over time. Mania ($p = 0.08$), Sydenham's Chorea ($p = 0.06$), Acrophobia ($p = 0.1$), Insomnia ($p = 0.1$), Body Dysmorphic Disorder ($p = 0.06$), Lethargy ($p = 0.1$), and PTSD ($p = 0.1$) marginally decreased, with significant decreases found in the first five days; Mania ($p = 0.039$), Sydenham's Chorea ($p = 0.034$), Acrophobic ($p = 0.048$), Insomnia ($p = 0.048$), Body Dysmorphic Disorder ($p = 0.034$), Lethargic ($p = 0.048$), and PTSD ($p = 0.048$) (**Figure 3** and **Table S2**).

Abnormal result values in **Table 1** are bolded. Results were positive for DNase antibody, Mycoplasma pneumoniae antibody IgG and IgM, EBV viral capsid AG, and EBV nuclear AG. Additionally, results revealed a vitamin D insufficiency and herpesvirus 6 antibody IgG, suggesting previous infection. While the titer of Strep at < 50 IUm appeared to be related to an earlier infection rather than active, the pediatrician diagnosed the patient's condition as PANDAS. A comprehensive list of blood/antibody testing is found in **Figure S1**.

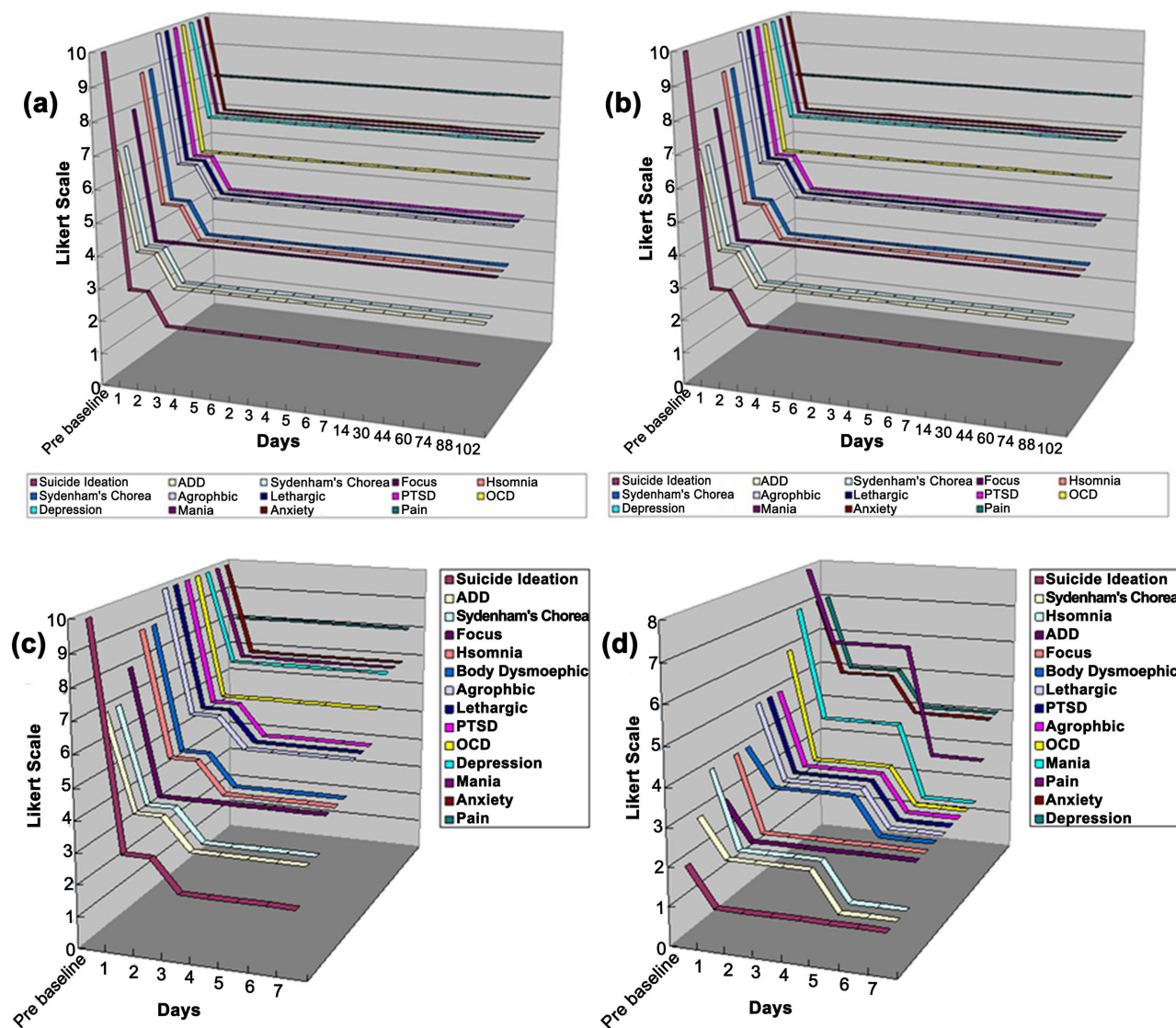


Figure 3. (a) shows the pro-dopamine regulation pre- and post-behavioral symptoms. (b) shows the antibacterial pre- and post-behavioral symptoms. (c) shows the first seven consecutive days for the pro-dopamine regulation pre- and post-behavioral symptoms. (d) shows the first seven consecutive days for the antibacterial pre- and post-behavioral symptoms.

4. Discussion

This case study is the first to test GARS with precision matched KB220 pro-dopamine regulation as a frontline treatment of PANDAS/CANS in a hypodopaminergic comprised adolescent with polymorphic dopamine D2 (-DRD2/ANKK (Taq1A)), OPRM1 (A/G), DRD3 (C/T), and MAOA (4R) risk alleles. These polymorphic risk alleles impact many RDS behaviors [17] presently observed in this patient. The innovative GARS system can successfully stratify the risk for developing RDS, which can be helpful for individuals in recovery or, in the present case, for those with full-blown RDS behaviors [15] [17].

Extreme RDS-like behaviors can co-occur with Strep and Lyme infection, especially in young people with DNA-induced hypodopaminergia [18]. Furthermore,

there is limited treatment and unbiased research available for PANDAS and CANS [19]. Antibacterial therapy for PANDAS has yielded some success, yet there is no such treatment for CANS since it is not the result of bacterial insult. Moreover, antibacterial therapies only provide a modest relief of symptoms over time. In spite of the diagnosis of PANDAS by the attending pediatrician and the positive response to antibacterial therapy, it is indeed possible that this patient's case could be classified as CANS. Since the titer for Streptococcal was below the active infection level, while Lyme was at an active titer level, while not certain, the pediatrician's diagnosis seems prudent.

Indeed, another caveat relates to the use and even further development of the GARS as a novel methodology to deliver customized or even semi-customized KB220. While it is true that there are common variants in the general population, it is also true that those who carry RDS have a significantly higher prevalence of at least eight out of ten variants, as measured by GARS [20]. DNA customization is important with the use of KB220, and most people with RDS (87%) require the Polygen formula of KB220 described above.

Nevertheless, if our findings hold up with the required double-blinded studies and an increased number of cases, certainly in terms of clinical practice, a quicker relief that could be maintained early on (dopamine homeostasis [21]) seems most prudent. Our recommendation, as such, is to utilize a combined therapeutic approach. The frontline utilization of GARS coupled with precision pro-dopamine KB220 variants following antibody diagnosis of bacterial infection (Strep/Lyme) may become a real futuristic option following more investigation. It should also be coupled with products containing glutathione, perilla, cumin, luteolin, fisetin, and others known to reduce neuroinflammatory processes.

In summary, treatment of neuropsychiatric symptoms with precision-guided DNA testing and pro-dopamine regulation in a genetically hypodopaminergic preadolescent male with putative PANDAS/CANS yielded a positive clinical outcome, suggesting epigenetic repair. It is noteworthy that one of us (DE) found similar benefits in treating teens diagnosed with PANDAS with precision KB220 variants, which will be the subject of a subsequent follow-up article [22]-[32].

5. Limitations

This study is limited by sample size and a non-conventional treatment approach. A more extensive controlled study is required to confirm the significance of these findings. An inherent bias in the self-reported data by the three-way agreement of the family members must be considered. Furthermore, the diagnosis of PANDAS needs to be questioned since the streptococcal titer was below the required active level in spite of a positive titer for Lyme. It is also possible that the time differential between first utilizing the KB220 variant and the putative diagnosis of PANDAS, was reflected by the presence of antibodies to previous streptococcal infection, which might explain the improvement with antibacterial therapy (see results). One might also consider the possibility of testing plasma dopamine levels pre and

post treatment especially with the Pro-dopamine regulation regime as administered in this case. However, it is difficult to distinguish peripheral vs brain dopamine in plasma levels. The most reliable way to test brain dopamine levels is via intrathecal testing [33]. This latter methodology is very difficult, especially for our youth.

We suggest herein that in the future, larger population RTC's should utilize GARS testing coupled with mRNA profiling, as we published previously [34]. We are also cognizant of racial genetic polymorphic differences, and this must also be taken into consideration [35]. Interestingly, even if we can't ensure a clear diagnosis of PANDAS *per se*, a diagnosis of CANS seems parsimonious. We incorporated the term "epigenetic" to infer environmentally induced manipulation of the core neurotransmitter signaling, but in the present study, we have not actually shown any effect on histone post-translational alteration in terms of methylation conversion to acetylation, the subject of another experiment.

The GARS test, in general, assesses the possibility of benefit from medication-assisted treatment with dopamine amplification. RDS methodology possesses a strong promise for diminishing the burden of hypodopaminergia by guiding the restoration of dopamine homeostasis, which could also affect any circadian rhythm insults [36]-[38].

While these initial results are encouraging, of course, more research is required, especially double-blinded placebo-controlled studies comparing antibacterial therapy alone, KB220 therapy alone [36], and coupling of the two modalities. Until these studies are completed, we must be cautious regarding any clinically relevant interpretation of these results [39].

Moreover, in the method section, we specified that a p-value of less than 5% was considered statistically significant for each test. However, regarding the FWER (family-wise error rate) control, we have not applied the Bonferroni correction since it is known as unsuitable for pilot/exploratory studies, which are intended to generate hypotheses and not confirm them.

6. Conclusion

Our recommendation, albeit possibly biased, is to utilize and further research a combined therapeutic approach, involving precision-guided DNA testing, pro-dopamine regulation along with antibacterial therapy, and anti-neuroinflammation agents in patients with suspected PANDAS/CANS.

Conflicts of Interest

K.B. is the inventor of GARS and KB220 variants and is credited with domestic and foreign issued and pending patents. D.H. was a paid consultant. The other authors declare no conflict of interest, financial or otherwise.

Author Contributions

Conceptualization: K.B.; methodology: K.B. and D.H.; formal analysis: D.H.;

investigation: K.B. and M.P.; writing—original draft preparation: K.B. and C.H.; writing—review and editing: K.B., M.P., D.H., D.B., A.G., S.K., J.K., B.W.D., D.B., A.B., T.M., R.D.B., E.J.M., P.K.T., D.E., C.A.D., E.R.B. and M.S.G.; supervision: K.B.; project administration: A.G. All authors have read and agreed to the published version of the manuscript. It is to be noted that while this is a case report, because of the uniqueness of the treatment and the controversy of the disorder, our team arduously worked together to present a clear but concise manuscript, including a review of the subject matter.

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Supplemental Figures

Accession #: [REDACTED] Client Info. [REDACTED]
 Lab: [REDACTED]
 Patient: [REDACTED]
 Pat. Chart No.: [REDACTED]
 Ordering Phys: [REDACTED]

Lab Order No.: [REDACTED] Collected: [REDACTED]
 Print Date: [REDACTED] Received: [REDACTED]
 Report Status: [REDACTED] Reported: [REDACTED]

Test Name	Flag	Result Value (Unit)	Reference Range	Lab
CBC (INCLUDES DIFF/PLT)				
WHITE BLOOD CELL COUNT		6.8 (Thousand/uL)	4.5-13.5	NL1
RED BLOOD CELL COUNT		5.09 (Million/uL)	4.00-5.20	NL1
HEMOGLOBIN		13.6 (g/dL)	11.5-15.5	NL1
HEMATOCRIT		40.2 (%)	35.0-45.0	NL1
MCV		79.0 (fL)	77.0-95.0	NL1
MCH		26.7 (pg)	25.0-33.0	NL1
MCHC		33.8 (g/dL)	31.0-36.0	NL1
RDW		13.1 (%)	11.0-15.0	NL1
PLATELET COUNT		267 (Thousand/uL)	140-400	NL1
MPV		11.1 (fL)	7.5-12.5	NL1
ABSOLUTE NEUTROPHILS		4277 (cells/uL)	1500-8000	NL1
ABSOLUTE LYMPHOCYTES		1822 (cells/uL)	1500-6500	NL1
ABSOLUTE MONOCYTES		571 (cells/uL)	200-900	NL1
ABSOLUTE EOSINOPHILS		82 (cells/uL)	15-500	NL1
ABSOLUTE BASOPHILS		48 (cells/uL)	0-200	NL1
NEUTROPHILS		62.9 (%)		NL1
LYMPHOCYTES		26.8 (%)		NL1
MONOCYTES		8.4 (%)		NL1
EOSINOPHILS		1.2 (%)		NL1
BASOPHILS		0.7 (%)		NL1
Comprehensive Metabolic Panel				
Glucose		89 (mg/dL)	65-99	NL1
Note: Fasting reference interval				
Urea Nitrogen (bun)		13 (mg/dL)	7-20	NL1
Creatinine		0.47 (mg/dL)	0.30-0.78	NL1
Note: Patient is <18 years old. Unable to calculate eGFR.				
Bun/creatinine Ratio		NOT APPLICABLE ((calc))	6-22	NL1
Sodium		139 (mmol/L)	135-146	NL1
Potassium		4.0 (mmol/L)	3.8-5.1	NL1
Chloride		103 (mmol/L)	98-110	NL1
Carbon Dioxide		25 (mmol/L)	20-32	NL1
Calcium		10.0 (mg/dL)	8.9-10.4	NL1
Protein, Total		7.0 (g/dL)	6.3-8.2	NL1
Albumin		4.6 (g/dL)	3.6-5.1	NL1
Globulin		2.4 (g/dL (calc))	2.1-3.5	NL1
Albumin/globulin Ratio		1.9 ((calc))	1.0-2.5	NL1
Bilirubin, Total		0.4 (mg/dL)	0.2-1.1	NL1
Alkaline Phosphatase		244 (U/L)	123-426	NL1
Ast		24 (U/L)	12-32	NL1

Page 1 continued on 2

Accession #: [REDACTED] Client Info: [REDACTED]
 Lab: [REDACTED]
 Patient: [REDACTED]
 Pat. Chart No.: [REDACTED]
 Ordering Phys: [REDACTED]

Alt	20 (U/L)	8-30	NL1
ANTI-STREPTOLYSIN O			
ANTI-STREPTOLYSIN O	<50 (IU/mL)	<250	NL1
MYCOPLASMA PNEUMONIAE ANTIBODIES (IGG, IGM)			
Mycoplasma Pneumoniae Antibody (igg)	H 1.71	<=0.90	AMD
Note:			
Reference Range:			
	<=0.90	Negative	
	0.91-1.09	Equivocal	
	>1.10	Positive	
A positive IgG result indicates that the patient has antibody to Mycoplasma. It does not differentiate between an active or past infection. The clinical diagnosis must be interpreted in conjunction with the clinical signs and symptoms of the patient.			
Mycoplasma Pneumoniae Antibody (igm)	671 (U/mL)	<770	AMD
Note:			
Reference Range:			
	<770 U/ml	Negative	
	770-950 U/mL	Low positive	
	>950 U/mL	Positive	
A positive IgM antibody result is consistent with recent infection. However, a negative result does not necessarily rule out recent infection as some individuals may not mount another IgM response, if previously infected.			
A positive IgM antibody result with or without a positive IgG antibody result, is consistent with recent infection. However, a negative result does not necessarily rule out recent infection as some individuals may not mount another IgM response, if previously infected. A positive IgG antibody result in the absence of a positive IgM antibody result, indicates that the patient has antibody to Mycoplasma. It does not differentiate between an active or past infection. The clinical diagnosis must be interpreted in conjunction with the clinical signs and symptoms of the patient.			
DNASE B ANTIBODY			
DNASE B ANTIBODY	H 622 (U/mL)	<376	SLI
HOMOCYSTEINE			
HOMOCYSTEINE	5.3 (umol/L)	<11.4	NL1
Note: Homocysteine is increased by functional deficiency of folate or vitamin B12. Testing for methylmalonic acid differentiates between these deficiencies. Other causes of increased homocysteine include renal failure, folate antagonists such as methotrexate and phenytoin, and exposure to nitrous oxide. Selhub J, et al., Ann Intern Med. 1999;131(5):331-9.			
TSH			
TSH	1.10 (mIU/L)	0.50-4.30	NL1
T3, FREE			
T3, FREE	4.3 (pg/mL)	3.3-4.8	NL1
T4, FREE			
T4, FREE	1.0 (ng/dL)	0.9-1.4	NL1

Accession #: [REDACTED] Client Info: [REDACTED]
 Lab: [REDACTED]
 Patient: [REDACTED]
 Pat. Chart No.: [REDACTED] [REDACTED] [REDACTED] [REDACTED]
 Ordering Phys: [REDACTED] [REDACTED]

GAD65, IA-2, AND INSULIN AUTOANTIBODY

Glutamic Acid Decarboxylase 65 Ab <5 (U/mL) <5 EZ

Note: This test was performed using the GAD65 ELISA method which is standardized against the International reference preparation 97/550.

Ia-2 Antibody <5.4 (U/mL) <5.4 EZ

Note: This test was performed using the IA-2 Antibody ELISA method which is standardized against the WHO Reference Reagent 97/550. The reference range reported was established specifically for this test method.

Insulin Autoantibody <0.4 (U/mL) <0.4 EZ

C-REACTIVE PROTEIN

C-REACTIVE PROTEIN 0.8 (mg/L) <8.0 NL1

(CMV) CYTOMEGALOVIRUS ANTIBODIES (IGG, IGM)

Cytomegalovirus Antibody (igg) <0.60 (U/mL) NL1

Note:

U/mL	Interpretation
-----	-----
<0.60	Negative
0.60-0.69	Equivocal
> or = 0.70	Positive

A positive result indicates that the patient has antibody to CMV. It does not differentiate between an active or past infection.

Cytomegalovirus Antibody (igm) <30.00 (AU/mL) NL1

Note:

AU/mL	Interpretation
-----	-----
<30.00	No Antibody Detected
30.00-34.99	Equivocal
> or = 35.00	Antibody Detected

Results from any one IgM assay should not be used as a sole determinant of a current or recent infection. Because an IgM test can yield false positive results and low level IgM antibody may persist for more than 12 months post infection, reliance on a single test result could be misleading. Acute infection is best diagnosed by demonstrating the conversion of IgG from negative to positive. If an acute infection is suspected, consider obtaining a new specimen and submit for both IgG and IgM testing in two or more weeks.

EPSTEIN BARR VIRUS ANTIBODY PANEL

EBV VIRAL CAPSID AG (VCA) <36.00 (U/mL) NL1

Note:

U/mL	Interpretation
-----	-----
<36.00	Negative
36.00-43.99	Equivocal
>43.99	Positive

EBV VIRAL CAPSID AG (VCA) H 220.00 (U/mL) NL1

Note:

U/mL	Interpretation
-----	-----
<18.00	Negative
18.00-21.99	Equivocal
>21.99	Positive

EBV NUCLEAR AG (EBNA) H >600.00 (U/mL) NL1

Note:

U/mL	Interpretation
-----	-----
<18.00	Negative
18.00-21.99	Equivocal
>21.99	Positive

[REDACTED]

Accession #: [REDACTED] Client Info.: [REDACTED]
 Lab: [REDACTED]
 Patient: [REDACTED]
 Pat. Chart No.: [REDACTED] [REDACTED] [REDACTED] [REDACTED]
 Ordering Phys: [REDACTED] [REDACTED]

INTERPRETATION: NL1

Note:
 Suggestive of a past Epstein-Barr virus infection. In infants, a similar pattern may occur as a result of passive maternal transfer of antibody.

HSV 1/2 IGG,TYPE SPECIFIC AB

HSV 1 IGG, TYPE SPECIFIC <0.90 (index) NL1
 HSV 2 IGG, TYPE SPECIFIC <0.90 (index) NL1

Note:	Index	Interpretation
	-----	-----
	<0.90	Negative
	0.90-1.09	Equivocal
	>1.09	Positive

This assay utilizes recombinant type-specific antigens to differentiate HSV-1 from HSV-2 infections. A positive result cannot distinguish between recent and past infection. If recent HSV infection is suspected but the results are negative or equivocal, the assay should be repeated in 4-6 weeks. The performance characteristics of the assay have not been established for pediatric populations, immunocompromised patients, or neonatal screening.

HERPESVIRUS 6 ANTIBODIES (IGG,IGM)

HERPESVIRUS 6 AB (IGG) H 1:10 (titer) TXC
 HERPESVIRUS 6 AB (IGM) <1:20 (titer) TXC
 INTERPRETATION PAST INFECTION TXC

Note:
 REFERENCE RANGE:
 IgG <1:10
 IgM <1:20

Human Herpesvirus 6 (HHV-6) infects T-lymphocytes, and has been identified as an etiologic agent of exanthema subitum. Rises in antibody titers to HHV-6 have been detected during infection with other viruses. In seroepidemiology studies of the prevalence of exposure using serum screening dilutions of 1:10, the detection of IgG antibody in a mid-life population approaches 100%. Due to this high prevalence of HHV-6 antibody, correlations of single IgG titers with specific diseases are of little clinical value.

Evidence of acute infection or reactivation of HHV-6 is demonstrated by a significant rise or seroconversion of IgG and IgM titers.

This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Infectious Disease. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

VITAMIN B12

VITAMIN B12 818 (pg/mL) 260-935 NL1

[REDACTED]

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Accession #: [REDACTED] Client Info: [REDACTED]
Lab: [REDACTED]
Patient: [REDACTED]
Pat. Chart No.: [REDACTED]
Ordering Phys: [REDACTED]

VITAMIN D, 25-OH, TOTAL, IA

VITAMIN D,25-OH,TOTAL,IA L 25 (ng/mL) 30-100 NL1

Note: Vitamin D Status 25-OH Vitamin D:

Deficiency: <20 ng/mL
Insufficiency: 20 - 29 ng/mL
Optimal: > or = 30 ng/mL

For 25-OH Vitamin D testing on patients on D2-supplementation and patients for whom quantitation of D2 and D3 fractions is required, the QuestAssureD(TM) 25-OH VIT D, (D2,D3), LC/MS/MS is recommended: order code 92888 (patients >2yrs). See Note 1

Note 1

For additional information, please refer to <http://education.QuestDiagnostics.com/faq/FAQ199> (This link is being provided for informational/educational purposes only.)

Performing Laboratory Information:

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]



www.igenex.com

TO : [Redacted]

Laboratory Director: [Redacted]

REFERRING PHYSICIAN

[Redacted]

[Redacted]

Collected: [Redacted]
 Received: [Redacted]
 Reported: [Redacted]
 Reprinted: [Redacted]
 Amended: [Redacted]
 Corrected: [Redacted]

TEST	SPECIMEN	RESULT	REFERENCE RANGE	UNITS
------	----------	--------	-----------------	-------

BORRELIOSIS - Lyme Disease

Lyme Western Blot IgM Serum
 IGX Criteria: Negative
 CDC/NYS Criteria: Negative

Band (kDa)	18	23-25*	28	30	31*	34*	39*	41*	45	58	66	83-93*
Intensity	-	-	-	-	-	-	-	IND	-	-	-	-

Band Intensity: Positive: + to +++++, Indeterminate: Ind, Negative: (-)

INTERPRETATION	IGX CRITERIA	CDC/NYS CRITERIA
Positive	2 or more of the starred bands are present (+): 23-25*, 31*, 34*, 39*, 41*, 83-93* kDa	2 of the following bands are present (+): 23-25*, 39*, and 41* kDa
Indeterminate	When only bands 31* and 41* kDa or only 31* and 83-93* are present, test 488 is recommended for confirmation	N/A
Negative	If only 41* and 93* kDa are present. Does not meet IGX criteria for a positive or indeterminate test result.	Does not meet CDC/NYS criteria for a positive or indeterminate test result.

Limitation: Bands 31* and 34* kDa are present in Lyme vaccinated patients. Viral antibodies cross react with antigens present at band positions 31* and 83-93* kDa.

Diagnosis should not be based on laboratory results alone. Results should be interpreted in conjunction with clinical symptoms and patient history.
 NOTE: Western Blots, ImmunoBlots, Lyme Dot Blot, Epitope, PCR, IFA, FISH, C. pneumoniae IgG/IgA, CD57, IGXSpot, Broad Coverage Antibody, COVID-19 Test - These tests were developed and their performance characteristics determined by IGeneX, Inc. They have not been cleared or approved by the FDA. The FDA has determined that such approval is not necessary. These tests are used for clinical purposes and should not be regarded as investigational or for research. IGeneX, Inc. is licensed by CMS and NYS to perform high complexity clinical laboratory testing.

Collected:
 Received:
 Reported:
 Reprinted:
 Amended:
 Corrected:

TEST	SPECIMEN	RESULT	REFERENCE RANGE	UNITS
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Lyme Western Blot IgG Serum
 IGX Criteria: **Positive**
 CDC/NYS Criteria: **Negative**

Band (kDa)	18	23-25*	28	30	31*	34*	39*	41*	45	58	66	83-93*
Intensity	-	-	+	-	-	++	-	+	-	-	-	-

Band Intensity: Positive: + to +++, Indeterminate: Ind, Negative: (-)

INTERPRETATION	IGX CRITERIA	CDC/NYS CRITERIA
Positive	2 or more of the starred bands are present (+): 23-25*, 31*, 34*, 39*, 41*, 83-93* kDa	5 or more of the following bands are present (+): 18, 23-25*, 28, 30, 39*, 41*, 45, 58, 66, 83-93* kDa
Indeterminate	Only bands 31* and 41* kDa are present, test 489 is recommended for confirmation	N/A
Negative	Does not meet IGX criteria for a positive or indeterminate test result.	Does not meet CDC/NYS criteria for a positive or indeterminate test result.

Limitation: Bands 31* and 34* kDa are present in Lyme vaccinated patients. Viral antibodies cross react with antigens present at band positions 31* and 83-93* kDa.

BABESIOSIS

TEST	SPECIMEN	RESULT	REFERENCE RANGE	UNITS
B. microti IFA - IgM	Serum	<20	< 20 : Negative = 20 : May or may not indicate active infection >=40 : Indicates active infection	Titer

Diagnosis should not be based on laboratory results alone. Results should be interpreted in conjunction with clinical symptoms and patient history.
 NOTE: Western Blots, ImmunoBlots, Lyme Dot Blot, Epitope, PCR, IFA, FISH, C. pneumoniae IgG/IgA, CD57, IGXSpot, Broad Coverage Antibody, COVID-19 Test - These tests were developed and their performance characteristics determined by iGeneX, Inc. They have not been cleared or approved by the FDA. The FDA has determined that such approval is not necessary. These tests are used for clinical purposes and should not be regarded as investigational or for research. iGeneX, Inc. is licensed by CMS and NYS to perform high complexity clinical laboratory testing.

Collected:
 Received:
 Reported:
 Reprinted:
 Amended:
 Corrected:

TEST	SPECIMEN	RESULT	REFERENCE RANGE	UNITS
B. microti IFA - IgG	Serum	<40	< 40 : Negative < 160 : May or may not suggest active infection >=160 : Indicates active infection	Titer
Babesia FISH	W blood	Negative		
B. duncani IFA - IgM	Serum	<20	< 20 : Negative = 20 : May or may not indicate active infection >=40 : Indicates active infection	Titer
B. duncani IFA - IgG	Serum	<40	< 40 : Negative < 160 : May or may not suggest active infection >=160 : Indicates active infection	Titer
<u>EHRlichiosis</u>				
HME IFA - IgM	Serum	<20	< 20 : Negative = 20 : May or may not indicate active infection >=40 : Indicates active infection	Titer
HME IFA - IgG	Serum	<40	< 40 : Negative < 160 : May or may not suggest active infection >=160 : Indicates active infection	Titer
<u>ANAPLAsmosis</u>				

Diagnosis should not be based on laboratory results alone. Results should be interpreted in conjunction with clinical symptoms and patient history.

NOTE: Western Blots, ImmunoBlots, Lyme Dot Blot, Epitope, PCR, IFA, FISH, C. pneumoniae IgG/IgA, CD57, IGXSpot, Broad Coverage Antibody, COVID-19 Test - These tests were developed and their performance characteristics determined by iGeneX, Inc. They have not been cleared or approved by the FDA. The FDA has determined that such approval is not necessary. These tests are used for clinical purposes and should not be regarded as investigational or for research. iGeneX, Inc. is licensed by CMS and NYS to perform high complexity clinical laboratory testing.

Collected:
 Received:
 Reported:
 Reprinted:
 Amended:
 Corrected:

TEST	SPECIMEN	RESULT	REFERENCE RANGE	UNITS
HGA IFA - IgM	Serum	<20	< 20 : Negative = 20 : May or may not indicate active infection >=40 : Indicates active infection	Titer
HGA IFA - IgG	Serum	<40	< 40 : Negative < 160 : May or may not suggest active infection >=160 : Indicates active infection	Titer
<u>RICKETTSIOSIS</u>				
R. rickettsii IFA - IgG	Serum	<40	< 40 : Negative < 160 : May or may not suggest active infection >=160 : Indicates active infection	Titer
R. typhi IFA - IgG	Serum	<40	< 40 : Negative < 160 : May or may not suggest active infection >=160 : Indicates active infection	Titer

End of Report

Diagnosis should not be based on laboratory results alone. Results should be interpreted in conjunction with clinical symptoms and patient history.

NOTE: Western Blots, ImmunoBlots, Lyme Dot Blot, Epitope, PCR, IFA, FISH, C, pneumonise IgG/IgA, CD57, IGXSpot, Broad Coverage Antibody, COVID-19 Test - These tests were developed and their performance characteristics determined by iGeneX, Inc. They have not been cleared or approved by the FDA. The FDA has determined that such approval is not necessary. These tests are used for clinical purposes and should not be regarded as investigational or for research. iGeneX, Inc. is licensed by CMS and NYS to perform high complexity clinical laboratory testing.

Figure S1. A comprehensive list of the patient's blood test results, including antibody titers.

Supplemental Tables

Table S1. Pro-dopamine regulation pre- and post-behavioral symptoms (Likert Scale 1 - 10). Stopped at week 30 and subsequently began antibacterial therapy.

Days	Depression	Suicide Ideation	Mania	OCD	ADD	Sydenham's Chorea	Anxiety	Agoraphobic	Insomnia	Pain	Body Dysmorphic Disorder	Lethargic	PTSD	Focus
Pre-baseline	10	10	10	10	7	7	10	10	9	8	9	10	10	8
1	7	3	7	6	4	4	7	6	5	8	5	6	6	4
2	7	3	7	5	4	4	7	6	6	8	4	6	6	4
3	7	2	7	6	3	3	7	5	4	8	4	5	5	4
4	7	2	7	6	3	3	7	5	4	8	4	5	5	4
5	7	2	7	6	3	3	7	5	4	8	4	5	5	4
6	7	2	7	6	3	3	7	5	4	8	4	5	5	4
2	7	2	7	6	3	3	7	5	4	8	4	5	5	4
3	7	2	7	6	3	3	7	5	4	8	4	5	5	4
4	7	2	7	6	3	3	7	5	4	8	4	5	5	4
5	7	2	7	6	3	3	7	5	4	8	4	5	5	4
6	7	2	7	6	3	3	7	5	4	8	4	5	5	4
7	7	2	7	6	3	3	7	5	4	8	4	5	5	4
14	7	2	7	6	3	3	7	5	4	8	4	5	5	4
30	7	2	7	6	3	3	7	5	4	8	4	5	5	4
44	7	2	7	6	3	3	7	5	4	8	4	5	5	4
60	7	2	7	6	3	3	7	5	4	8	4	5	5	4
74	7	2	7	6	3	3	7	5	4	8	4	5	5	4
88	7	2	7	6	3	3	7	5	4	8	4	5	5	4
102	7	2	7	6	3	3	7	5	4	8	4	5	5	4

Table S2. Antibacterial pre- and post-behavioral symptoms (Likert Scale 1 - 10). The antibacterial therapy that was tolerated by the patient and prescribed by the attending physician throughout the entire treatment course included Augmentin 875 - 125 mg BID, Bactrim 800 - 160 mg BID, Doxycycline 100 mg BID, and Cefdinir 300 mg BID.

Days	Depression	Suicide Ideation	Mania	OCD	ODD	Sydenham's Chorea	Anxiety	Agoraphobic	Insomnia	Pain	Body Dysmorphic Disorder	Lethargic	PTSD	Focus
Pre-baseline	7	2	7	6	3	3	7	5	4	8	4	5	5	4
1	5	1	4	3	2	2	5	3	2	6	3	3	3	2
2	5	1	4	3	2	2	5	3	2	6	3	3	3	2

Continued

3	5	1	4	3	2	2	5	3	2	6	3	3	3	2
4	4	1	4	3	2	2	4	3	2	6	3	3	3	2
5	4	1	2	2	2	1	4	2	1	3	2	2	2	2
6	4	1	2	2	2	1	4	2	1	3	2	2	2	2
7	4	1	2	2	2	1	4	2	1	3	2	2	2	2
14	4	1	2	2	2	1	4	2	1	3	2	2	2	2
30	4	1	2	2	2	1	4	2	1	3	2	2	2	2
44	4	1	2	2	2	1	4	2	1	3	2	2	2	2
60	4	1	2	2	2	1	4	2	1	3	2	2	2	2
74	3	1	2	2	2	1	3	2	1	2	2	2	2	2
