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Pediatric Acute Neuropsychiatric Syndrome: IVIG Therapy and Costs to Treat

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My name is Roger H. Kobayashi from Omaha, Nebraska where I am Senior Consultant to Allergy, Asthma & Immunology Associates in Omaha/Lincoln Nebraska and have evaluated approximately 140 patients with PANS/PANDAS over the course of approximately 15 years. I am board certified in Allergy/Immunology and was previously Head of Allergy/Immunology at the University of Nebraska Medical Center, Head of the Pediatric Allergy Clinic at UCLA and on the faculty at UCLA for the past 32 years. My research interests are Antibody Immune Deficiencies, access to affordable health care and currently, interventions in severe CoVID infections in outlying rural centers. I have approximately 170 publications [approximately 40 on IVIG/SCIG] and abstracts and have lectured in Europe, Asia, the Middle East and Central America. I am here to give an overview of the use of IVIG with reference to its cost. I am also attaching background information [see attached] on the use of IVIG on PANS.

Summary: i] IVIG is very expensive ii] PANS children may respond favorably to IVIG [90% according to PANS Consortium] iii] Children should have moderate to severe symptoms iv] Diagnosis must comply with NIH criteria v] Doctors highly experienced should evaluate or consult on child if possible vi] More than one infusion may be required vii] objective evidence of severity BEFORE infusion and objective evidence of improvement after infusion[s] must be demonstrated.

1. What is PANS/PANDAS:

PANS IS A DISORDER BASED ON CLINICAL AND OBSERVATIONAL CRITERIA.

a] Described by Sir William Osler in 1896, but current description by NIH, Stanford and Johns Hopkins investigators. Clinical description of "sudden onset" of an acute behavior disorder characterized by 1] TICS/OCD/eating abnormalities 2] associated concurrent "sudden onset" symptoms [at least two…see table] but most commonly anxiety, erratic emotional behavior, behavioral regression, sensory abnormalities. 3] no laboratories studies distinguish PANS.

It is most commonly seen by Pediatricians, referred to psychiatrists/behavioral specialists/ neurologists. Less commonly they are referred to Infectious Disease, Rheumatology or Immunology specialists. The onset is typically between the ages of 7 and 11, although some are seen at a younger age or in the teenage years. Since it is a behaviorally defined clinical diagnosis, all other causes must be "ruled out" before PANS can be diagnosed. This is being modified as experience is gained, i.e. PANS is suspected earlier in the course and treated earlier than previously.

b] An immunologic/autoimmune cause is postulated for PANS, where malfunctioning immune response is misdirected against the brain [basal ganglia] resulting in sudden, bizarre behavior.

c] Laboratory studies: there are *NO GOOD LABORATORY* studies to diagnose PANS. Bacterial/viral titers are circumstantial/associative and auto-antibodies as well as immune activation markers are circumstantial and not necessarily definitive. These include Gr. A strep, Cunningham Panel and

markers for autoimmune encephalitis. Our group has a manuscript [in press] where we looked at 77 different laboratory studies and *none were definitive* for syndrome activity.

d] Psychiatric and psychological measurements: there are a number of psychological and behavioral tests which are used to measure behavioral/syndrome abnormalities such as the Yale-Brown Obsessive Compulsive Behavioral Scale, tests for depression, anxiety, memory et al. In our clinic, we employ a simplified, abbreviated questionnaire which semi-quantitates clinical status.

e] PANS should be a multi-specialty disease managed primarily by Pediatricians, psychiatrists and neurologists, with the outside help of rheumatologists, infectious disease, ENT and immunologists. These children are extremely complex and it is impossible for one doctor to take care. Also, these children put enormous stress on families and schools. As these children require so much time and effort, many doctors will not see them or will close their practices to these children.

2. Treatment of PANS/PANDAS

Please see my UCLA Grand Round Slides on PANS/PANDAS and treatment.

a] Behavioral and counseling is critical to managing this disorder. The help of the school is also important, since these children put enormous stress on the teachers, their classmates and the school system. Most of the referrals to our clinic come from this sector as well as from Pediatricians.

b] Psychiatric and neurology evaluation is important in managing these children. Anti-anxiety, anti-depression, anti-TIC medications are often employed. Most often, it is the failure of these medications that will result in referral to Immunologists.

c] Other medications: 1] anti-inflammatory – steroids, NSAIDs, immune modulators, anti-histamines and others have been used. Very potent medications such as rituximab, cyclosporine and others have been used, but in my strong opinion, should be used only by those in University Medical Centers where protocols might be in place.

d] IVIG:

Please see our slides from the European Academy of Pediatrics presentation and an abbreviated, preliminary copy [1st 4 pages] of our manuscript submitted for publication but not yet accepted.

1] IVIG is a highly concentrated, highly purified, very safe biological comprised of IgG antibodies derived from human plasma [1%]. b] It was first approved by the FDA for use in the United States in 1981 for the treatment of Primary Immunodeficiency Diseases to replace antibodies which these patients did not have. c] In 1982, Paul Imbach and associates from Switzerland treated children with ITP and with this landmark discovery, a whole new arena of therapy, i.e. the use of IVIG for its anti-inflammatory and immune modulating effects, opened up. d] More gammaglobulin [*70%*] is used in non-immunodeficient patients , with neurologic diseases utilizing the majority of product. Other patients receiving IVIG include those with blood disorders [ITP et al], cancer and severe skin diseases. e] While tens of millions of grams of IVIG/SCIG are manufactured every year, the demand for these products has outstripped supply. There were shortages in 2019 and again in 2020.

e] Main diseases where IVIG/SCIG are used: 1] Primary Immune Deficiency [XLA/CVID and other antibody deficiencies as well as other mixed immunodeficiencies] 2] Neurologic Diseases – Guillian Barr'e Syndrome, CIDP, Stiff Person Syndrome and off label other neurologic diseases including seizures, autoimmune encephalitis and PANS/PANDAS 3] other autoimmune auto-inflammatory diseases including Gastrointestinal, Dermatologic, Renal, infectious diseases.

2] ***IVIG is expensive, costing approximately $5,000 to $15,000 per treatment for PANS. Cost is the main barrier to treatment.***

Cost per gram: $81 to $120/gram ASP Hospitals and infusion centers may charge 1 to 5 times this price
Supplies: range from $200 to $300 per infusion
Nursing time: $150/hour Three to 6 hours ➔ $450 to $900 per infusion
Facility charges: ~$200 - $500 per infusion

Example: Child 40 kg [88 pounds] would receive between 40 gms [1 gm/kg/dose] and 80 gms [2 gms/kg/dose]. If receiving 2 gms/kg, this would require two days infusion per month.

Low end charges: $4,000-$8,000 ASP for product, supplies/infusion = $250/hr, nursing time = $750/infusion [5 hours], facility charges/infusion = $350 Total costs/treatment = $5,350 to $10,700 Emphasize: these are the LOW END charges.

Other considerations: a] Site of infusion: home infusion generally less expensive. Hospital most expensive. b] infusion service company critical: some are reasonable and some unfortunately are not. c] IVIG product price varies d] out of pocket costs vary depending on insurance coverage. e] if services not covered, the non-negotiated maximum price is charged to the patient which can be substantial.

Example of 20 year old treated for neuropathy who had three different insurance coverage in one year. https://weinfuse.com/infusion-billing-confusion/

Insurance Company	Rate Charged	Amount Written Off	Amount the Hospital Received
GEHA (Aetna Contract)	$28,405.99	$7,669.62	$20,736.37*
Blue Cross Alabama	$29,756.15	$25,930.71	$3,827.45
Cigna	$28,755.17	$25,436.17	$3,319.00**

*$4,260.90 was what I (the patient) had to pay ** $221.82 was what I had to pay

As an aside, IVIG in high doses are being used experimentally in severe CoVID 19 infections and synthesized monoclonal antibodies against CoVID are currently being employed against CoVID➔ Regeneron and Eli Lilly.

f] High Dose IVIG for the treatment of PANS/PANDAS has been used since the late 1990's and several publications on its possible benefit have appeared:
There have been *three prospective*, but non-placebo controlled studies done, one by Dr. Swedo's group at the NIH, an Italian group and our group. All three studies showed benefit, but the main criticism has been about patient selection, lack of controls [placebo group] and lack of biologic markers [lab tests]. These are valid arguments, but placebo controlled groups are very hard to do in psychiatrically affected, highly anxious children [IVIG infusions over two days, 6 to 10 hours at a time] and specific laboratory tests for autoimmune, autoinflammatory diseases are very difficult, even in well established diseases.

g] Our findings [*see European slides for details*]:
1] 21 moderate to severe PANS affected children, refractory to conventional treatment [psychiatric medications/counseling/antibiotics and oral anti-inflammatory medications including steroids] 2] extensive pretesting [6 different validated psychometric tests Y-BOCS, etc before, during and after treatment, clinical and laboratory tests [77 different blood tests] were done. 3] Six treatments with high dose IVIG [1000 mg/kg/dose] were given at 3 week intervals 4] independent psychologic evaluation for testing, interviews and interpretation were done [the principal investigators had no direct contact with psychologists to insure complete objectivity].

Results:
***all 21 patients received significant benefit* from HDIVIG in terms of psychometric instrument results, clinical improvement as assessed by doctors and parents, BUT NO GOOD CORRELATION WITH BLOOD**

STUDIES WERE SEEN. There was one test which correlated, but since it is considered experimental, it was not included in our paper and is being published separately in an immunologic manuscript.

Our results were presented at European [EAP/ESID] and American Annual Meetings [CIS/AAP] and the American Academy of Neurology [they don't like PANS].

Summary: HDIVIG may be beneficial for some patients with intractable PANS where auto-inflammation may be present. More than one dose may be required and at the present time I do not know which children will respond, but many do and it is the prime obligation of the physician to help patients.