Functional Neurology Anatomy and Central Neurological Pathways

Dr. Brandon Brock

FUNCTIONAL NEUROLOGY SEMINARS

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National University of Health Sciences

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Basal Ganglia
Key Clinical Concepts

1. What are the general functions of the basal ganglia?

2. What are the clinical presentations of basal ganglia disorders?

3. What are mechanisms that cause basal ganglia disorders?
What are the general functions of the basal ganglia?
Learning Exercise

Perform finger-to-nose task

- What does the frontal cortex do?
- What does the cerebellum do?
- What does the basal ganglia do?
  - Direct pathway
  - Indirect pathway
Key Clinical Concepts

What are the clinical presentations of basal ganglia disorders?
Movement disorders

The expanding universe of disorders of the basal ganglia

Jose A Obeso, Maria C Rodriguez-Oroz, Maria Stamelou, Kaliche P Bhatia, David J Boon

The basal ganglia were originally thought to be associated purely with motor control. However, dysfunction and pathology of different regions and circuits are now known to give rise to many clinical manifestations beyond the association of basal ganglia dysfunction with movement disorders. Moreover, disorders that were thought to be caused by dysfunction of the basal ganglia only, such as Parkinson's disease and Huntington's disease, have diverse abnormalities distributed not only in the sensorimotor but also in the limbic systems; this knowledge poses new questions and challenges. We discuss advances and the unanswered questions, and ways in which progress might be made.

Introduction

In modern clinical practice, the basal ganglia refers mainly to the striatum, the internal and external globus pallidus, the subthalamic nucleus, and the substantia nigra pars compacta and pars reticulata because of their close anatomical connectivity and pathophysiological implications (figure 1). The basal ganglia were implicated in the origin of movement disorders by Wilson's observations 100 years ago that lesions of the lenticular nucleus were associated with dystonia and parkinsonism1 and that focal lesions of the subthalamic nucleus and substantia nigra pars compacta caused hemichorea-ballism2 and parkinsonism.3

In his seminal Croonian lecture in 1925, Wilson stated: "I have found no reason to modify in any important respect...that the main features of disease of the corpus striatum consist of disorders of muscle tone regulation and the appearance of involuntary movements". The recognition that Parkinson's disease arises as a consequence of degeneration of the substantia nigra pars compacta and loss of striatal dopamine reinforced this idea. Marsden subsequently concluded that "on the basis of the motor deficits observed in patients with Parkinson's disease, the basal ganglia normally are responsible for the automatic execution of learned motor plans". In the mid-1980s, the emergence of a basal ganglia model4 (figure 2), which focused on the pathophysiology of parkinsonism and dyskinesias, further strengthened the association between the basal ganglia and abnormal movements. During the past two decades, robust evidence has accumulated that the basal ganglia are intimately connected with the cortex through several segregated but parallel loops (figure 1), which have been subdivided into motor, associative (cognitive), and limbic (emotional) domains.5 They deal, respectively, with the control of movement, behaviour and cognition, and reward and emotions. These features have also been documented for the striatum and subthalamic nucleus by MRI in people.6

Accordingly, dysfunction in any one of these circuits can give rise to movement disorders, behavioural and cognitive abnormalities, and mood changes.

Movement disorders

Two fundamental disorders of muscle activation in the absence of paraesthesia or weakness are linked to disorders of the basal ganglia (videos 3-5). First, the parkinsonian syndrome is characterized by poverty and slowness of movement (akinesia or bradykinesia) and typically associated with increased muscle tone (rigidity), giving rise to the akinetic-rigid or parkinsonian syndrome, which can also be accompanied by tremor at rest. Second, dyskinesias and hyperkinesias are movements characterized by excessive involuntary muscular activity that perturb voluntary motor commands, interfering with normal intended actions. These movements have two main forms: dystonia, in which long (100-500 ms) muscle spasms with co-contraction of antagonist muscles twist and distort the body into abnormal posture, while retaining the capacity to achieve the desired movement; and chorea, which consists of fragments of movements, often mimicking normal voluntary movements, but irregularly flowing from one body segment to another, causing a dance-like appearance. Ballism is typically associated with larger amplitudes and more proximal movements but is qualitatively similar to chorea. Levodopa-induced dyskinesias (chorea, dystonia) in patients with Parkinson's disease are the most common clinical cause of dyskinesias.

The akinetic-rigid syndrome, best represented by Parkinson's disease, is primarily related to cell loss in...
The expanding universe of disorders of the basal ganglia

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WATCH VIDEO PRESENTATION IN LIVESTREAM OR REPLAYS
Basal Ganglia
Anatomical Review
Basal Ganglia

- Cerebrum
- Caudate nucleus
- Claustrom
- Putamen
- Globus pallidus
- Pons
- Subthalamic nucleus
- Substantia nigra
- Mediodorsal and ventromedial nuclei of the thalamus

Together = corpus striatum
Basal Ganglia Anatomical Grouping

Basal Ganglia
- Corpus striatum
  - Substantia nigra
  - Subthalamic nucleus
    - (Amygdala = Limbic)
- Striatum (Neostriatum)
  - Caudate
  - Putamen
    - Globus pallidus
      - Lenticular nucleus
        - Internal segment
        - External segment
Basal Ganglia Anatomical Grouping

Basal Ganglia
  - Corpus striatum
    - Striatum (Neostriatum)
      - Caudate
      - Putamen
      - Globus pallidus
        - Internal segment
        - External segment
          - Lenticular nucleus
  - Substantia nigra
  - Subthalamic nucleus
    -(Amygdala = Limbic)
Basal Ganglia
Schematic illustration showing interrelationship of thalamus, lentiform nucleus, caudate nucleus, and amygdaloid body (viewed from side).
Basal Ganglia
Direct and Indirect Pathways
**INDIRECT PATHWAY**

- decreases excitatory thalamic input to cortex
- TURNS DOWN motor activity

**Diagram Details:**
- Motor Cortex
- Corticostriate
- Striatum (caudate/putamen)
- Globus pallidus
- Subthalamic nucleus
- Ansa lenticularis-Lenticular fasciculus
- VA-VL Motor thalamus
- Lateral Corticospinal Tract (LCST)
- LMN: Muscles
- Pyramidal decussation
- CST: Corticospinal Tract
DOPAMINE EXCITES THE DIRECT AND INHIBITS THE INDIRECT PATHWAY

THE EFFECT OF THE DOPAMINERGIC NIGROSTRIATAL PROJECTION IS TO INCREASE MOTOR ACTIVITY

Substantia Nigra Dopaminergic

Turns UP the Direct Pathway (D1)
Turns DOWN the Indirect Pathway (D2)
INCREASED VA/VL drive to cortex
MORE MOTOR ACTIVITY
THE EFFECT OF THE CHOLINERGIC STRIATAL INTERNEURONS IS TO DECREASE MOTOR ACTIVITY

ACH TURNS DOWN MOTOR ACTIVITY
ACH inhibits striatal cells in the direct loop
ACH excites striatal cells in the indirect loop

DA TURNS UP MOTOR ACTIVITY
DA excites striatal cells in the direct loop via D₁ receptors
DA inhibits striatal cells in the indirect loop via D₂ receptors
CEREBRAL CORTEX: PRIMARILY SMA, 6, 4, 8

(+) GLU

S.NIGRA → DOPA → STRIATUM → D1 RECEPTORS

COMPACTA

(+)

DOPA → S.NIGRA

→ COMPACTA

(-) GABA

substance P

DIRECT PATHWAY

LATERAL GLOBUS PALLIDUS

INDIRECT PATHWAY

(-) GABA

MEDIAL GLOBUS PALLIDUS (And S. Nigra Reticularis)

(-) GABA

VENTRAL LATERAL NUCLEUS THALAMUS (And ventral anterior Nucleus of Thalamus)

(+)

GLU

CEREBRAL CORTEX: PRIMARILY SMA, 6, 4, 8
Functional Neuroanatomy of the Basal Ganglia

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Basal Ganglia Loops
Basal Ganglia Loops

Recurrent temporal networks and language acquisition—from corticostriatal neurophysiology to reservoir computing
Neuromodulation for Obsessive–Compulsive Disorder

Sensorimotor and premotor cortex

Dorsolateral prefrontal and lateral orbitofrontal cortex

Limbic and paralimbic cortex, hippocampus and amygdala

(a) Motor circuit
(b) Associative circuit
(c) Limbic circuit

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Basal Ganglia
Somatotopic Organization
Somatotopic organization of the primate basal ganglia
Somatotopic organization of the primate basal ganglia
Reassessing Models of Basal Ganglia Function and Dysfunction

Alexandra B. Nelson\textsuperscript{1,2} and Anatol C. Kreitzer\textsuperscript{1,3}

7 Concepts for The Rate Model

1. The basal ganglia form an interconnected network
2. The basal ganglia are involved in not only motor function, but cognitive function
3. The cortex may generate motor or cognitive commands, but the execution and/or maintenance of these commands relies on the integrity of the basal ganglia as a positive feedback system to sustain activity
4. The network can be subdivided into two major pathways, the direct and indirect pathways
5. Dopamine differentially acts on the two major pathways at the level of the striatum
6. Among several possible actions, a subset are selected by striatum; competing actions are suppressed by lateral inhibition at several levels of the circuit
7. Network output is integrated at the level of the basal ganglia output nuclei, the GPi and SNr, which inhibit or disinhibit thalamocortical and/or brainstem areas to suppress or promote specific actions
Reassessing Models of Basal Ganglia Function and Dysfunction

Alexandra B. Nelson\textsuperscript{1,2} and Anatol C. Kreitzer\textsuperscript{1,3}

7 Concepts for Direct and Indirect Pathways

1. Dopamine has opposing physiological effects on the activity of striatal neurons composing the direct and indirect pathways

2. Ablation or inactivation of indirect pathway neurons should lead to increased or excessive movement

3. Ablation or inactivation of direct pathway neurons should lead to decreased movement

4. Activation of indirect pathway neurons should lead to decreased movement

5. Activation of direct pathway neurons should lead to increased or excessive movement

6. Decreases in basal ganglia output (at the level of the GPi or SNr) should correlate with increased movement

7. Increases in basal ganglia output (at the level of the GPi or SNr) should correlate with decreased movement
Basal Ganglia
Indirect Pathway
INDIRECT PATHWAY

decreases excitatory thalamic input to cortex

TURNS DOWN motor activity
Disorders of the Basal Ganglia: Hyperkinesia

Hemiballism
Subthalamic Nucleus lesion

Direct Pathway still turning activity UP
Indirect Pathway is DOWN
INCREASED VA/VL drive to cortex
MORE MOTOR ACTIVITY!!!
Disorders of the Basal Ganglia: Hyperkinesia

**Huntington's Chorea**
- ACh cells lost

**DIRECT PATHWAY**
- REM: direct turns UP movement
- ACh ↓ = Direct ↑ (dis-inhibition)

- MORE MOTOR ACTIVITY!!!

**INDIRECT PATHWAY**
- Rem: indirect turns DOWN movement
- ACh ↓ or Striatal-GP(ext)↓ = Indirect ↓

- MORE MOTOR ACTIVITY!!!
Motor Tic Disorder

WATCH VIDEO PRESENTATION IN LIVESTREAM OR REPLAYS
Sydenham’s Chorea

WATCH VIDEO PRESENTATION IN LIVESTREAM OR REPLAYS
Hemichorea--Hemiballism after Diabetic Ketoacidosis
Basal Ganglia
Direct Pathway
DIRECT PATHWAY

increases excitatory thalamic input to cortex

TURNS UP motor activity
Disorders of the Basal Ganglia: Hypokinesia

**Parkinson's Disease**
SN Dopamine cells lost

**DIRECT PATHWAY**
Remember: direct turns UP movement

Dopamine ↓ = direct pathway ↓
Dopamine excitation lost
ACh inhibition unopposed

LESS MOTOR ACTIVITY!!!
Basal Ganglia Direct Pathway Clinical Presentation

- Hypokinesia: slowness of movement
  - progression into difficulty into Initiation of Movement
    - progression into Freezing
- Hypomimia: hyptonic facial expression "masked face"
  - progression into reduced blinking and drooling
- Muscle Stiffness and Rigidity from lack of corticospinal inhibition of anterior horn cells at the spinal cord
- Hypomimia or Dysarthria from lack of motor activity to vocal musculature
- Constipation from lack of intestinal smooth muscle contracture

- progress to Reduced Arm Swing and loss of stride or Shuffling Gait and Writer's Cramp
  - progression to frozen shoulder or frozen hip syndromes
    - Inability to ambulate due to rigidity
Young Onset Parkinson's Disease

WATCH VIDEO PRESENTATION IN LIVESTREAM OR REPLAYS
https://doctorprodigious.wordpress.com
Parkinson’s Feature of Re-Emergent Tremor

WATCH VIDEO PRESENTATION IN LIVESTREAM OR REPLAYS
https://doctorprodigious.wordpress.com
Video Examples

UNIFIED PARKINSON'S DISEASE RATING SCALE

Hand Movements:

Right and Left
0-normal
1-mild slowing, and/or reduction in amp.
2-moderately impaired, definite and early fatiguing, may have occasional arrests
3-severely impaired, frequent hesitations and arrest
4-can barely perform
Unified Parkinson’s Disease Rating Scale

• Hand Movements
  • 0 = Normal
  • 1 = mild slowing, and/or reduction in amplitude
  • 2 = moderately impaired, definite and early fatiguing, may have occasional arrests
  • 3 = severely impaired, frequent hesitations and arrest
  • 4 = can barely perform
Parkinsonism is any condition that causes movement abnormalities as seen in PD. Must have 2 symptoms from list. Bradykinesia + muscle rigidity or tremor or postural instability.

Idiopathic Parkinson’s Disease:
- Primary pathology is dopamine deficiency.
- Good response to dopaminergic medications.
- Later in disease: falling, dementia

Atypical Parkinson’s = Parkinson’s Plus Syndromes:
- Minimal to no dopamine deficiency.
- Mild to no improvement with dopaminergic medications.
- Early in disease: falling, dementia

Secondary Parkinsonism due to:
- Medications
- Mini Strokes
- Normal Pressure Hydrocephalus
- Head trauma

Progressive Supranuclear Palsy (PSP)

Multiple Systems Atrophy (MSA) Early and more pronounced autonomic symptoms*,

Corticobasal Degeneration (CBD) Apraxia, limb dystonia

Lewy Body Dementia (LBD)

MSA -P
Dysautonomia* + PD symptoms
Old terms:
- Shy Drager
- (SND) Striatonigral Degeneration

MSA - C
Dysautonomia* + Cerebellar symptoms
Old term:
Olivopontocerebellar atrophy (OPCA)

*Autonomic symptoms:
- Orthostatic hypotension
- Constipation
- Urinary dysfunction
- Erectile dysfunction
Basal Ganglia
Hyperdirect Pathway
Key Clinical Concepts

What are mechanisms that cause basal ganglia disorders?
Neurodegenerative Diseases of the Basal Ganglia
Lewy body disease in Parkinson’s
**Lewy body disease in Parkinson’s**

*Parkinson disease, Lewy body:* The Lewy body is the pathological hallmark of Parkinson disease. The Lewy body inclusion shows an eosinophilic core surrounded by a pale halo (arrow). The protein alpha-synuclein is a component of the Lewy body.
Native α-syn (random coil) → Molecular chaperones → Misfolded proteins (β-pleated sheet) → Oligomers (β-pleated sheet) → Amyloid fibrils (β-pleated sheet) → Lewy neurite → Lewy body

Phagosomes and lysosomes → Autophagy → Proteasome → Peptides

- Oxidative stress
- Protein sequestration
- Disruption of axonal transport
- Synaptic dysfunction
- Inhibition of UPS
- Mitochondrial dysfunction
Degenerative Substantia Nigra in Parkinson’s Disease

The left shows Parkinson's disease with a pale substantia nigra compared to a normal tissue on the right.
Genetic Neurodegenerative Disorder – Huntington’s Disease

Microscopically, the caudate nucleus in Huntington's disease demonstrates loss of neurons along with gliosis.
Huntington's disease is shown grossly in this coronal section of the brain. It demonstrates atrophy of the caudate with resultant increase in size of lateral ventricles.
Lacunar Infarction of the Basal Ganglia
Lacunar Infarction and Small Vessel Disease: Pathology and Pathophysiology

Louis R Caplan
Division of Cerebrovascular Disease, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Two major vascular pathologies underlie brain damage in patients with disease of small size penetrating brain arteries and arterioles: 1) thickening of the arterial media and 2) obstruction of the origins of penetrating arteries by parent artery intimal plaques. The media of these small vessels may be thickened by fibrinoid deposition and hypertrophy of smooth muscle and other connective tissue elements that accompanies degenerative changes in patients with hypertension and or diabetes or can contain foreign deposits as in amyloid angiopathy and genetically mediated conditions such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. These pathological changes lead to 2 different pathophysiologicals: 1) brain ischemia in regions supplied by the affected arteries. The resultant lesions are deep small infarcts, most often involving the basal ganglia, pons, thalami and cerebral white matter and 2) leakage of fluid causing edema and later gliosis in white matter tracts. The changes in the media and adventitia effect metalloproteinases and other substances within the matrix of the vessels and lead to abnormal blood/brain barriers in these small vessels and chronic gliosis and atrophy of cerebral white matter.

Keywords: Cerebral small vessel diseases; CADASIL; Cerebral amyloid angiopathy; Pathophysiology

Pathology

Vascular pathology

Two major vascular pathologies underlie brain damage in patients who have important abnormalities involving small size penetrating brain arteries and arterioles: 1) thickening of the arterial media with encroachment on the arterial lumens and 2) obstruction of the origins of penetrating arteries by parent large intracranial artery intimal plaques. Hypertension, diabetes and other as yet undetermined genetic and other factors may promote thickening of the media of penetrating arteries by fibrinoid deposition and hypertrophy of smooth muscle and other connective tissue elements. The arterial media can also contain foreign deposits as in amyloid angiopathy and genetically mediated conditions such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Miller Fisher, nearly a half century ago, analyzed the arterial pathology that caused small deep infarcts by carefully assessing serial sections of vessels at necropsy. He observed that the penetrating arteries that supplied the territory of lacunar infarcts showed a characteristic vascular pathology. These tiny vessels often contained focal enlargements and small hemorrhagic extravasations through the walls of these arteries. Subintimal foam cells sometimes obliterated the lumens, and pink staining fibrinoid material was present within the vessel walls. The arteries in some regions were often replaced by whorls, tangles, and wisps of connective tissue that obliterated the usual vascular layers. Fisher called these processes segmental arterial disorganization, fibrinoid degeneration, and apoplexy. Figure 1, given to me by Fisher, shows a severely narrowed penetrating artery in a patient with severe hyperten-
The most common locations of these lacunar infarcts are the putamen and the pallidum, followed by the pons, thalamus, caudate nucleus, internal capsule, and corona radiata.
Lacunar infarct (<1cm): A relatively small cystic lesion in the putamen secondary to small vessel disease. Common locations for lacunes include basal ganglia, pons, internal capsule, thalamus and cerebral white matter.
Lacunar Infarcts

Figure 3. Drawing showing the arterial pathology in atheromatous branch disease: (A) plaque in parent artery obstructing a branch, (B) junctional plaque extending into the branch, (C) microatheroma formed at the orifice of a branch.
Mechanisms that Injure the Basal Ganglia
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s disease</td>
<td>7467</td>
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<tr>
<td>Vascular parkinsonism</td>
<td>816</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>616</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>562</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>332</td>
</tr>
<tr>
<td>Other cases of parkinsonism</td>
<td>314</td>
</tr>
<tr>
<td>Drug-induced parkinsonism</td>
<td>282</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>224</td>
</tr>
<tr>
<td>Hemiparkinsonism</td>
<td>85</td>
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<tr>
<td>Post-encephalitic parkinsonism</td>
<td>22</td>
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<tr>
<td>Carbon monoxide poisoning</td>
<td>9</td>
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<tr>
<td>Manganese poisoning</td>
<td>9</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>6</td>
</tr>
<tr>
<td>Familial basal ganglia calcification</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 1: Clinical diagnoses in 10,153 patients presenting with parkinsonism at Baylor College of Medicine, 1988–2013
Movement Disorders in Systemic Diseases

Werner Poewe, MD*, Atbin Djamshidian-Tehrani, MD

KEYWORDS
- Movement disorders • Systemic disease • Basal ganglia • Autoimmune disorders
- Metabolic disorders • Endocrine disorders • Paraneoplastic disorders
- Intoxications

KEY POINTS
- Movement disorders may be the harbinger of an underlying systemic disease.
- Careful neurologic examination, considering associated systemic features in combination with neuroimaging and laboratory tests, will help narrow down the differential diagnosis and may lead to the final diagnosis.
- Management will often involve a multidisciplinary team including neurologists and the primary care physician, but also allied health professionals, such as physical, occupational, and speech and language therapists.
- Unlike neurodegenerative movement disorders, those occurring in the setting of systemic diseases are frequently amenable to causal treatment of the underlying condition, thus making early correct diagnostic classification a key priority.
<table>
<thead>
<tr>
<th>Etiology</th>
<th>Movement Disorders</th>
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</thead>
<tbody>
<tr>
<td><strong>Infectious diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Whipple disease</td>
<td>Oculo-masticatory myorhythmia</td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>Parkinsonism, chorea</td>
</tr>
<tr>
<td>CNS-tuberculosis</td>
<td>Tremor, chorea, myoclonus, dystonia, and parkinsonism</td>
</tr>
<tr>
<td>HIV</td>
<td>Hemichorea, tremor, parkinsonism, dystonia</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Hemichorea-hemiballism</td>
</tr>
<tr>
<td>Neurocysticercosis</td>
<td>Generally rare: parkinsonism, hemichorea</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Parkinsonism</td>
</tr>
<tr>
<td><em>Streptococcus</em> infection</td>
<td>Parkinsonism, Sydenham-chorea (children)</td>
</tr>
<tr>
<td><strong>Autoimmune disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Chorea, Parkinsonism rare</td>
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<tr>
<td>Sjögren syndrome</td>
<td>Parkinsonism</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>Rare: Parkinsonism, chorea</td>
</tr>
<tr>
<td>Stiff person syndrome</td>
<td>Hyperlordosis, ataxia</td>
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<tr>
<td>Neuro- Behêt</td>
<td>Chorea, ataxia</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Ataxia, parkinsonism, chorea</td>
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<tr>
<td><strong>Paraneoplastic disorders</strong></td>
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<tr>
<td>Anti-Yo/ACPA</td>
<td>Ataxia, tremor</td>
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<tr>
<td>Anti-NMDAR encephalitis</td>
<td>Dystonia, orofacial dyskinesias, ballism, myorhythmia</td>
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<tr>
<td>Amphiphysin</td>
<td>Stiff person syndrome (hyperlordosis, rigidity, ataxia)</td>
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<tr>
<td>Anti-Hu/ANNA-1</td>
<td>Dystonia, chorea, tremor, parkinsonism</td>
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<tr>
<td>CV2/CRMP5</td>
<td>Chorea, dystonia, ataxia</td>
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<tr>
<td>Ma1/Ma2</td>
<td>Parkinsonism</td>
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<tr>
<td>Hu/ANNA-2/VGKC</td>
<td>Myoclonus</td>
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<td>Tr</td>
<td>Ataxia</td>
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<tr>
<td>Ri/ANNA-2</td>
<td>Dystonia, parkinsonism (PSP-like), opsodonus-myoclonus</td>
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<td>VGCC</td>
<td>Ataxia</td>
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<tr>
<td><strong>Metabolic</strong></td>
<td></td>
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<tr>
<td>Wilson disease</td>
<td>Dystonia, parkinsonism, “wing-beating” tremor</td>
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<td>Acquired hepatocerebral degeneration</td>
<td>Orobulucogingual dyskinesias, parkinsonism</td>
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<td>Hemochromatosis</td>
<td>Ataxia, tremor, parkinsonism</td>
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<tr>
<td>Renal failure</td>
<td>Asterixis, restless legs syndrome, Parkinsonism rare</td>
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<td><strong>Endocrine</strong></td>
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<tr>
<td>Nonketotic hyperglycemia</td>
<td>Hemichorea-hemiballism, asterixis</td>
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<tr>
<td>Hypoglycemia</td>
<td>Paroxysmal chorea</td>
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<tr>
<td>Hyperthyroidism</td>
<td>Tremor, chorea</td>
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<td>Hypothyroidism</td>
<td>Parkinsonism</td>
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<td>Hypoparathyroidism</td>
<td>Parkinsonism, ataxia, tremor</td>
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<td><strong>Hematological</strong></td>
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<tr>
<td>Polycythemia rubra vera</td>
<td>Chorea</td>
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<tr>
<td>Condition</td>
<td>Symptom(s)</td>
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<tr>
<td>-----------------------------------------</td>
<td>------------------------------------------------</td>
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<tr>
<td>Chorea acanthocytosis</td>
<td>Chorea, feeding dystonia</td>
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<td>McLeod syndrome</td>
<td>Chorea</td>
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<tr>
<td>Lysosomal storage disease</td>
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<tr>
<td>Gaucher</td>
<td>Parkinsonism, dystonia</td>
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<td>Niemann-Pick C</td>
<td>Parkinsonism, supranuclear vertical gaze palsy, dystonia</td>
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<tr>
<td>Metal and nonmetal systemic intoxication</td>
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<tr>
<td>Carbon monoxide</td>
<td>Parkinsonism</td>
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<td>Manganese</td>
<td>Parkinsonism</td>
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<td>MPTP</td>
<td>Parkinsonism</td>
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<td>Ephedrine</td>
<td>Parkinsonism</td>
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<td>Carbon monoxide</td>
<td>Parkinsonism</td>
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<tr>
<td>Carbon disulfide</td>
<td>Parkinsonism</td>
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<tr>
<td>Cyanide</td>
<td>Parkinsonism, dystonia, apraxia of eyelid opening</td>
</tr>
<tr>
<td>Toluene</td>
<td>Parkinsonism</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Ataxia, parkinsonism</td>
</tr>
<tr>
<td>Thallium</td>
<td>Chorea</td>
</tr>
</tbody>
</table>
Table 3
Other common systemic autoimmune disorders causing movement disorders

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Movement Disorder</th>
<th>Diagnostic Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid-responsive autoimmune encephalitis</td>
<td>Tremor (80%)</td>
<td>Antithyroglobulin antibodies</td>
</tr>
<tr>
<td>(Hashimoto)</td>
<td>Ataxia and gait disorder (66%)</td>
<td>Antithyroperoxidase antibodies</td>
</tr>
<tr>
<td></td>
<td>Myoclonus (37%)</td>
<td>MRI brain scan</td>
</tr>
<tr>
<td></td>
<td>Cognitive impairment (36%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychiatric problems (30%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Strokelike episodes</td>
<td></td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Cerebellar ataxia</td>
<td>Antigliadin antibodies</td>
</tr>
<tr>
<td></td>
<td>Polyneuropathy</td>
<td>Anti-TG2 antibodies</td>
</tr>
<tr>
<td></td>
<td>Myelopathy</td>
<td>Anti-TG6 antibodies</td>
</tr>
<tr>
<td></td>
<td>Chorea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parkinsonism</td>
<td></td>
</tr>
<tr>
<td>Behçet disease</td>
<td>Chorea</td>
<td>MRI brain scan (basal ganglia hyperintensities)</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
<td>Cerebrospinal fluid</td>
</tr>
</tbody>
</table>

Table 4  
Common paraneoplastic movement disorders

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Associated Antibodies</th>
<th>Movement Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian teratoma</td>
<td>NMDAR</td>
<td>Chorea</td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>CV2/CRMP5</td>
<td></td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>Hu/ANNA-1</td>
<td></td>
</tr>
<tr>
<td>Ovarian teratoma</td>
<td>NMDAR</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>CV2/CRMP5</td>
<td></td>
</tr>
<tr>
<td>Small-cell lung cancer, breast, gyn</td>
<td>Hu/ANNA-1</td>
<td></td>
</tr>
<tr>
<td>Small-cell lung cancer, breast, gyn</td>
<td>Ri/ANNA-2</td>
<td>Atypical parkinsonism</td>
</tr>
<tr>
<td>Testis, non-small-cell lung cancer</td>
<td>Ma1/Ma2</td>
<td></td>
</tr>
<tr>
<td>Small-cell lung cancer, breast, gyn</td>
<td>Ri/ANNA-2</td>
<td>Stiff person syndrome</td>
</tr>
<tr>
<td>B-cell lymphoma</td>
<td>Hu/ANNA-1</td>
<td></td>
</tr>
<tr>
<td>Small-cell lung cancer, breast</td>
<td>Amphiphysin</td>
<td>Orofacial dyskinesia</td>
</tr>
<tr>
<td>Ovarian teratoma</td>
<td>NMDAR</td>
<td>Opsoclonus-myoclonus</td>
</tr>
<tr>
<td>Small-cell lung cancer, breast</td>
<td>Ri/ANNA-2</td>
<td>Myoclonus</td>
</tr>
<tr>
<td>Breast</td>
<td>Hu/ANNA-2</td>
<td></td>
</tr>
<tr>
<td>Various different tumors</td>
<td>VGKC</td>
<td></td>
</tr>
<tr>
<td>Breast, gyn</td>
<td>Yo/APCA</td>
<td>Ataxia</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>Tr</td>
<td></td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>VGCC</td>
<td></td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>Amphiphysin</td>
<td></td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>CV2/CRMP5</td>
<td></td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small-cell lung cancer</td>
<td>Hu/ANNA-1</td>
<td>Tremor</td>
</tr>
<tr>
<td>Ovarian, breast</td>
<td>Yo/APCA</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3. T2-weighted MRI shows bilateral basal ganglia lesions in a patient with carbon monoxide poisoning.

Carbon monoxide poisoning: During the first few hours after carbon monoxide poisoning, the brain is swollen, congested and cherry-red. After 24-48 hours of survival, scattered petechial hemorrhages may be seen in white matter with larger hemorrhages in the pallidum (arrows).
Pesticide Induced Destruction of Basal Ganglia

WATCH VIDEO PRESENTATION IN LIVESTREAM OR REPLAYS
### Table 14.1

Environmental toxicants associated with parkinsonism

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Exposure setting(s)</th>
<th>Mechanism(s) of action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dieldrin</td>
<td>Occupational, diet</td>
<td>Dopamine mishandling, generation of reactive oxygen species (ROS)</td>
<td>Corrigan et al. (1996, 2000); Kitazawa et al. (2001); Kamel et al. (2007); Hatcher et al. (2008)</td>
</tr>
<tr>
<td>Chlorpyrifos</td>
<td>Occupational</td>
<td>Alteration in dopamine signaling</td>
<td>Dhillon et al. (2008); Gatto et al. (2009); Torres-Altoro et al. (2011)</td>
</tr>
<tr>
<td>Rotenone</td>
<td>Occupational</td>
<td>Inhibition of mitochondrial complex I</td>
<td>Betarbet et al. (2000); Dhillon et al. (2008); Tanner et al. (2011)</td>
</tr>
<tr>
<td>Paraquat</td>
<td>Occupational</td>
<td>Generation of ROS</td>
<td>Thiruchelvam et al. (2000b); Manning-Bog et al. (2002); McCormack et al. (2002); Kamel et al. (2007); Tanner et al. (2011)</td>
</tr>
<tr>
<td>Polychlorinated biphenyls (PCBs)</td>
<td>Occupational, diet</td>
<td>Dopamine mishandling</td>
<td>Seegal et al. (1994); Corrigan et al. (1998, 2000); Caudle et al. (2006); Steenland et al. (2006); Hatcher-Martin et al. (2012)</td>
</tr>
<tr>
<td>Iron</td>
<td>Occupational, diet</td>
<td>Generation of ROS</td>
<td>Gorell et al. (1997); Gerlach et al. (2006); Kaur et al. (2007)</td>
</tr>
<tr>
<td>Manganese</td>
<td>Occupational</td>
<td>Generation of ROS, NMDA-mediated excitotoxicity, mitochondrial inhibition</td>
<td>Gavin et al. (1999); Guilarte et al. (2006); Racette et al. (2012)</td>
</tr>
<tr>
<td>Trichloroethylene (TCE)</td>
<td>Occupational</td>
<td>Generation of ROS, inhibition of mitochondrial complex I</td>
<td>Gash et al. (2008); Liu et al. (2010); Goldman et al. (2012)</td>
</tr>
</tbody>
</table>
Elevated levels of antibodies against xenobiotics in a subgroup of healthy subjects

Aristo Vojdani\textsuperscript{a*}, Datis Kharrazian\textsuperscript{b} and Partha Sarathi Mukherjee\textsuperscript{c}

ABSTRACT: In spite of numerous research efforts, the exact etiology of autoimmune diseases remains largely unknown. Genetics and environmental factors, including xenobiotics, are believed to be involved in the induction of autoimmune disease. Some environmental chemicals, acting as haptens, can bind to a high-molecular-weight carrier protein such as human serum albumin (HSA), causing the immune system to misidentify self-tissue as an invader and launch an immune response against it, leading to autoimmunity. This study aimed to examine the percentage of blood samples from healthy donors in which chemical agents mounted immune challenges and produced antibodies against HSA-bound chemicals. The levels of specific antibodies against 12 different chemicals bound to HSA were measured by ELISA in serum from 400 blood donors. We found that 10\% (IgG) and 17\% (IgM) of tested individuals showed significant antibody elevation against aflatoxin-HSA adduct. The percentage of elevation against the other 11 chemicals ranged from 8\% to 22\% (IgG) and 13\% to 18\% (IgM). Performance of serial dilution and inhibition of the chemical–antibody reaction by specific antigens but not by non-specific antigens were indicative of the specificity of these antibodies. Although we lack information about chemical exposure in the tested individuals, detection of antibodies against various protein adducts may indicate chronic exposure to these chemical haptens in about 20\% of the tested individuals. Currently the pathological significance of these antibodies in human blood is still unclear, and this protein adduct formation could be one of the mechanisms by which environmental chemicals induce autoimmune reactivity in a significant percentage of the population. Copyright © 2014. The Authors. Journal of Applied Toxicology Published by John Wiley & Sons Ltd.
Elevated levels of antibodies against xenobiotics in a subgroup of healthy subjects.
Vojdani A¹, Kharrazian D, Mukherjee PS.
The Potential Roles of Bisphenol A (BPA) Pathogenesis in Autoimmunity.

Kharrazian D1.

BPA

BPA-binding protein

BPA binds to host protein

New antigen

Antibody produced for new antigen

Antibody also now reacts to host protein

Autoimmunity
Elevated levels of antibodies against xenobiotics in a subgroup of healthy subjects.

Vojdani A\(^1\), Kharrazian D, Mukherjee PS.
Elevated levels of antibodies against xenobiotics in a subgroup of healthy subjects.

Vojdani A¹, Kharrazian D, Mukherjee PS.
### Toxic Effects profiles

#### 1760 Chlorinated Pesticides & PCB Profile - Serum

**Methodology:** Gas Chromatography/Mass Spectrometry

<table>
<thead>
<tr>
<th>Chlorinated Pesticides</th>
<th>Results</th>
<th>95th Percentile**</th>
<th>Lipid Adjusted Results</th>
<th>95th Percentile**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DDE</strong></td>
<td>Detected</td>
<td>12.10</td>
<td>74.6</td>
<td>1860</td>
</tr>
<tr>
<td><strong>DDT</strong></td>
<td>Not Detected</td>
<td>0.13</td>
<td>N/A</td>
<td>19.5</td>
</tr>
<tr>
<td><strong>Dieldrin</strong></td>
<td>Not Detected</td>
<td>0.14</td>
<td>N/A</td>
<td>19.0</td>
</tr>
<tr>
<td><strong>Heptachlor Epoxide</strong></td>
<td>Not Detected</td>
<td>0.13</td>
<td>N/A</td>
<td>18.0</td>
</tr>
<tr>
<td><strong>Hexachlorobenzene (HCB)</strong></td>
<td>Not Detected</td>
<td>0.10</td>
<td>N/A</td>
<td>28.0</td>
</tr>
<tr>
<td><strong>Mirex</strong></td>
<td>Not Detected</td>
<td>0.09</td>
<td>N/A</td>
<td>13.2</td>
</tr>
<tr>
<td><strong>Oxychlordane</strong></td>
<td>Not Detected</td>
<td>0.27</td>
<td>N/A</td>
<td>37.7</td>
</tr>
<tr>
<td><strong>trans-Nonaclor</strong></td>
<td>Not Detected</td>
<td>0.47</td>
<td>N/A</td>
<td>68.3</td>
</tr>
<tr>
<td><strong>Endosulfan Sulfate</strong></td>
<td>Not Detected</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

#### Polychlorinated Biphenyls (PCBs)

**Dioxin-like Polychlorinated Biphenyls**

<table>
<thead>
<tr>
<th>PCB</th>
<th>Results</th>
<th>95th Percentile**</th>
<th>Lipid Adjusted Results</th>
<th>95th Percentile**</th>
</tr>
</thead>
<tbody>
<tr>
<td>118</td>
<td>Not Detected</td>
<td>0.22</td>
<td>N/A</td>
<td>31.3</td>
</tr>
<tr>
<td>120</td>
<td>Not Detected</td>
<td>0.00048</td>
<td>N/A</td>
<td>0.069</td>
</tr>
<tr>
<td>150</td>
<td>Not Detected</td>
<td>0.10</td>
<td>N/A</td>
<td>15.3</td>
</tr>
<tr>
<td>109</td>
<td>Not Detected</td>
<td>0.00027</td>
<td>N/A</td>
<td>0.041</td>
</tr>
</tbody>
</table>

**Non-Dioxin-like Polychlorinated Biphenyls**

<table>
<thead>
<tr>
<th>PCB</th>
<th>Results</th>
<th>95th Percentile**</th>
<th>Lipid Adjusted Results</th>
<th>95th Percentile**</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td>Not Detected</td>
<td>0.16</td>
<td>N/A</td>
<td>22.3</td>
</tr>
<tr>
<td>138</td>
<td>Detected</td>
<td>0.48</td>
<td>Detected</td>
<td>76.3</td>
</tr>
<tr>
<td>133</td>
<td>Detected</td>
<td>0.08 - 0.18**</td>
<td>14.0 - 44.7**</td>
<td></td>
</tr>
<tr>
<td>153</td>
<td>Detected</td>
<td>0.02</td>
<td>Detected</td>
<td>97.1</td>
</tr>
<tr>
<td>180</td>
<td>Not Detected</td>
<td>0.53</td>
<td>N/A</td>
<td>81.5</td>
</tr>
<tr>
<td>77f</td>
<td>Not Detected</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### ARRAY 11

**Chemical Immune Reactivity Screen**

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Equivocal</th>
<th>Out of Range</th>
<th>Numeric Value</th>
<th>Reference (ELISA Index)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoxin IgG+IgA</td>
<td></td>
<td>X</td>
<td></td>
<td>0.46</td>
<td>0.4-1.8</td>
</tr>
<tr>
<td>Aflatoxin IgM</td>
<td></td>
<td>X</td>
<td></td>
<td>0.46</td>
<td>0.1-1.5</td>
</tr>
<tr>
<td>Formaldehyde+Glutaraldehyde IgG+IgA</td>
<td></td>
<td>X</td>
<td></td>
<td>0.33</td>
<td>0.3-1.4</td>
</tr>
<tr>
<td>Formaldehyde+Glutaraldehyde IgM</td>
<td></td>
<td>X</td>
<td></td>
<td>0.21</td>
<td>0.1-1.5</td>
</tr>
<tr>
<td>Isocyanate IgG+IgA</td>
<td></td>
<td>X</td>
<td></td>
<td>0.48</td>
<td>0.1-1.1</td>
</tr>
<tr>
<td>Isocyanate IgM</td>
<td></td>
<td>X</td>
<td></td>
<td>0.47</td>
<td>0.1-1.2</td>
</tr>
<tr>
<td>Trimellitic+Phthalic Anhydrides IgG+IgA</td>
<td></td>
<td>X</td>
<td></td>
<td>0.34</td>
<td>0.1-1.3</td>
</tr>
<tr>
<td>Trimellitic+Phthalic Anhydrides IgM</td>
<td></td>
<td>X</td>
<td></td>
<td>0.66</td>
<td>0.1-2.0</td>
</tr>
<tr>
<td>Benzene Ring Compounds IgG+IgA</td>
<td></td>
<td>X</td>
<td></td>
<td>0.98</td>
<td>0.2-1.3</td>
</tr>
<tr>
<td>Benzene Ring Compounds IgM</td>
<td></td>
<td>X</td>
<td></td>
<td>0.45</td>
<td>0.1-1.6</td>
</tr>
<tr>
<td>BPA Binding Protein IgG+IgA</td>
<td></td>
<td>X</td>
<td></td>
<td>0.46</td>
<td>0.2-1.8</td>
</tr>
<tr>
<td>BPA Binding Protein IgM</td>
<td></td>
<td>X</td>
<td></td>
<td>0.32</td>
<td>0.1-1.8</td>
</tr>
<tr>
<td>Bisphenol A IgG+IgA</td>
<td></td>
<td>X</td>
<td></td>
<td>&gt;5.3</td>
<td>0.1-1.8</td>
</tr>
<tr>
<td>Bisphenol A IgM</td>
<td></td>
<td>X</td>
<td></td>
<td>4.52</td>
<td>0.1-2.0</td>
</tr>
<tr>
<td>Tetrabromobisphenol A IgG+IgA</td>
<td></td>
<td>X</td>
<td></td>
<td>1.47</td>
<td>0.1-1.6</td>
</tr>
<tr>
<td>Tetrabromobisphenol A IgM</td>
<td></td>
<td>X</td>
<td></td>
<td>1.99</td>
<td>0.2-2.0</td>
</tr>
<tr>
<td>Tetrachloroethylene IgG+IgA</td>
<td></td>
<td>X</td>
<td></td>
<td>3.22</td>
<td>0.4-2.0</td>
</tr>
<tr>
<td>Tetrachloroethylene IgM</td>
<td></td>
<td>X</td>
<td></td>
<td>1.12</td>
<td>0.1-2.4</td>
</tr>
<tr>
<td>Parabens IgG+IgA</td>
<td></td>
<td>X</td>
<td></td>
<td>1.45</td>
<td>0.2-1.7</td>
</tr>
<tr>
<td>Parabens IgM</td>
<td></td>
<td>X</td>
<td></td>
<td>2.22</td>
<td>0.1-1.5</td>
</tr>
<tr>
<td>Mercury Compounds IgG+IgA</td>
<td></td>
<td>X</td>
<td></td>
<td>1.36</td>
<td>0.1-1.5</td>
</tr>
<tr>
<td>Mercury Compounds IgM</td>
<td></td>
<td>X</td>
<td></td>
<td>1.87</td>
<td>0.1-2.1</td>
</tr>
<tr>
<td>Mixed Heavy Metals IgG+IgA</td>
<td></td>
<td>X</td>
<td></td>
<td>1.88</td>
<td>0.2-1.8</td>
</tr>
<tr>
<td>Mixed Heavy Metals IgM</td>
<td></td>
<td>X</td>
<td></td>
<td>1.89</td>
<td>0.1-1.8</td>
</tr>
</tbody>
</table>

All reference ranges are for demonstration purposes only. Final reference ranges will be published upon completion of validation process.

*Reference ranges are calculated based on the mean ± 2 standard deviations (SD). Results >1 SD, and <2 SDs above the mean are considered to be equivocal. An equivocal result represents the range between negative and suspicious low positive results. Results >2 SDs are considered out of range, and positive.
TOXICANT LOSS OF IMMUNE TOLERANCE, NEUROLOGIC DISEASE, AND NUTRITIONAL STRATEGIES

Datiss Kharrazian*
Bastyr University, San Diego, CA USA

ABSTRACT

This paper reviews immunology models of chemical tolerance and the role they may play with the pathogenesis of neurological autoimmune and neurodegenerative disease and how we may be able to reduce the impacts of these adverse reactions with various nutritional applications. The immune model of chemical tolerance describes how trace amounts of exposures to various chemicals commonly found within our environment lead to exaggerated immune responses turning on the cascade of immune dysregulation and systemic inflammation leading to neurological disease. Immune chemical tolerance is maintained by healthy integration of various immune cells that can be disrupted from toxicant exposure, chronic stress physiology, blood-brain barrier compromise, intestinal barrier compromise, hormone imbalances, antigenic models, oxidative stress models, and various mechanisms that induce loss of healthy immune integration. These mechanisms themselves have been shown to have the ability to be manipulated and modulated with various nutritional applications. With an increasing epidemic of toxicant load and virtually no conventional or pharmaceutical strategies to decrease their impacts on human systems evidence-based consideration leads us to the potential role of various natural compounds that exhibit activity that can decrease the expression NF-kappaB, optimize glutathione redox systems, improve barrier system impermeability, and support regulatory T-cell activity all which is essential to improve chemical immune tolerance environmental toxicants.

Keywords: Autoimmune, neurodegenerative disease, environment, chemical tolerance, oxidative stress, blood-brain barrier, nutrition

INTRODUCTION

There is no question that environmental pollution and toxins have potential for severe adverse impacts on both developmental brain health and inflammatory and autoimmune mechanisms of neurodegeneration [1]. We are living in a world that has changed dramatically within our lifetimes. We are now exposed to countless chemicals, hybridized foods, and genetically modified foods, all of which are very immune activating. Additionally, the increased use of pharmaceutical drugs is increasing rapidly. This polypharmacy model of various drugs potentially has diverse impacts on human physiology beyond known adverse reactions and iatrogenic causes of death and disability. The U.S consumption of foods known as the Standard American Diet (SAD) is not only very

*Correspondence: Dr. Datiss Kharrazian, 1001 Cañavateck Court Carlsbad, CA 92011 Email Datiss56@gmail.com
Infectious Destruction of Basal Ganglia

WATCH VIDEO PRESENTATION IN LIVESTREAM OR REPLAYS
Immune Cross-Reactivity of the Basal Ganglia – PANDAS

(Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus)
Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS): An Evolving Concept
Iron Accumulation Induced Destruction of the Basal Ganglia

WATCH VIDEO PRESENTATION IN LIVESTREAM OR REPLAYS
Globus Pallidus Iron Accumulation
Review

Neurodegeneration with brain iron accumulation — Clinical syndromes and neuroimaging

Hyman M. Schipper*

Centre for Neurotranslational Research, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada H3T 1E2
Department of Neurology & Neurosurgery, McGill University, Montreal, Quebec, Canada H3T 1E2
Department of Medicine, McGill University, Montreal, Quebec, Canada H3T 1E2

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Magnetic resonance imaging (MRI)
Neuroimaging
Syndromes

ABSTRACT

Iron participates in a wide array of cellular functions and is essential for normal neural development and physiology. However, if inappropriately managed, the transition metal is capable of generating neurotoxic reactive oxygen species. A number of hereditary conditions perturb body iron homeostasis and some, collectively referred to as neurodegeneration with brain iron accumulation (NBIA), promote pathological deposition of the metal predominantly or exclusively within the central nervous system (CNS). In this article, we discuss seven NBIA disorders with emphasis on the clinical syndromes and neuroimaging. The latter primarily entails magnetic resonance scanning using iron-sensitive sequences. The conditions considered are Friedreich ataxia (FA), pantothenate kinase 2-associated neurodegeneration (PKAN), PLA2G6-associated neurodegeneration (PLAN), FA2H-associated neurodegeneration (FAHN), Kufor-Rakeb disease (KRD), aceruloplasminemia, and neuroferritinopathy. An approach to differential diagnosis and the status of iron chelation therapy for several of these entities are presented. This article is part of a Special Issue entitled: Imaging Brain Aging and Neurodegenerative disease.

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Copper Toxicity (Wilson’s Disease)  
Destruction of the Basal Ganglia

WATCH VIDEO PRESENTATION IN LIVESTREAM OR REPLAYS
Wilson disease (hepatolenticular degeneration): Wilson disease is an autosomal recessive disorder caused by mutations in a copper transport gene (ATP7B). The putamen appears brown and shrunken. The caudate is often severely affected, but pallidum, thalamus and brain stem may be less severely involved.
Autoimmune Destruction of Basal Ganglia
Basal Ganglia and Nutritional Considerations
Nutritional and Dietary Considerations for Basal Ganglia Disorders

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Abstract

Various flavonoids, botanicals, nutrients, amino acids, sulfur compounds, pro-glutathione compounds have been shown to dampen the oxidative stress mechanisms of basal ganglia disorders in addition to various models of basal ganglia neurodegenerative mechanisms. Dietary associations with gluten sensitivity, celiac disease, caloric restriction, and intermittent fasting have also been evaluated in the dietary model of basal ganglia neurodegeneration. This article will review these nutritional and dietary interventions with basal ganglia disease.

Keywords: Basal Ganglia, Flavonoids, Botanicals, Nutrients, Amino Acids, Glutathione, Gluten Sensitivity, Caloric Restriction

Introduction

Disorders of the basal ganglia such as Parkinson's, dystonia, tics, restless leg syndrome, obsessive compulsive disorders, and numerous movement and cognitive disorders are common conditions in the current population however the use of dietary and nutritional supplementation has not been routinely implemented in the management of these conditions in the current healthcare model. The use of antioxidants either with dietary restrictions or nutrient supplementation has demonstrated potential
1. What are the general functions of the basal ganglia?

2. What are the clinical presentations of basal ganglia disorders?

3. What are mechanisms that cause basal ganglia disorders?