

# Brain differences in autism

## 1. The cerebellum

Autopsy and MRI studies have repeatedly and consistently found loss of Purkinje and granule cells of the cerebellum in autistic subjects. There is general agreement that this loss occurs before birth, probably in early pregnancy. There are two known possible causes: a specific genetic condition or an immune system response to a toxin or pathogen during pregnancy.

There is only one discovery in the history of autism research that has been found to be both unique and specific to the disorder, a loss of cerebellar Purkinje and granule cells occurring early in brain development and an immature development of the limbic system.

(Jansen R.A.; Melatonin, A look at Humoral Factors in the Cerebellum; Autism and Dev. Disabilities List 1997)

Dr. Courchesne: 'In ten autopsy cases (out of ten), there was Purkinje cell loss in the cerebellar hemisphere and in five of ten cases there was Purkinje cell loss in the cerebellar vermis. The magnetic resonance studies have found that there is a reduction in the size of the neocerebellar vermis and the neocerebellar hemisphere which is conclusive with the Purkinje cell loss' (Eric Courchesne, 1991).

'Due to the fact there is no evidence of atrophy or deterioration after full development and the results of MR images and autopsy studies, it is now believed that the neocerebellar loss occurs before birth.' (Autism; Audrey Abell)

### **The cerebellum can be divided into the following functional divisions:**

**Neocerebellum:** This is the phylogenetically newest part. It consists of the lateral lobes and is involved in fine movements and speech through major connections with the cerebral cortex.

**Paleocerebellum:** Through interconnections with the spinal cord, this part mediates sequential movements such as walking, running and swimming. It consists of the anterior and posterior vermis.

**Archicerebellum:** Its major connections are with the vestibular (balance) system. It consists of the flocculus, nodule and lingula and mediates general posture and eye movements.

The hemispheres are separated from one another by a thin structure called the vermis, or "worm". The vermis, located in the midline of the cerebellum, receives auditory and visual information from the tectum. It also receives cutaneous and kinesthetic information from the spinal chord. The vermis sends outputs to the fastigial nucleus, which outputs to the vestibular nucleus and to motor nuclei in the reticular formation.

### **Basic function of Cerebellum**

The cerebellum is involved in a feedback loop for muscle movement. When the cortex sends a message for motor movement to the lower motor neurons in the brain stem and spinal cord, it also sends a copy of this message to the cerebellum. In addition, information gets to the cerebellum from muscle spindles, joints and tendons. This information (proprioception and kinesthesia) lets the cerebellum know about the movements that have been executed, so that it can determine how well motor commands coming from the cortex are being carried out.

The role of the cerebellum is primarily in the co-ordination of complex movements, using inputs from hearing, balance, visual and muscular systems as well as from higher executive commands and emotional states. The messages reach the cerebellum through a complex web of millions of climbing fibers, which pulsate rhythmically, generating an awareness of self in space, of self in relation to other, of self in motion. The information is channeled along parallel fibers and Purkinje neurons tap into this information, sending back modulated information to the body and brain, enabling the execution of complex actions such as speech and non-verbal communication (body language).

### **Causes and mechanisms of Purkinje cell loss**

The indole alkaloids ibogaine and harmaline are beta-carboline derivatives that cause both hallucinations and tremor. We recently found that ibogaine induces a marked glial reaction in the cerebellum with activated astrocytes and microglia aligned in parasagittal stripes within the vermis. Based on those findings, the present study was conducted to investigate whether ibogaine may cause neuronal injury or degeneration. The results demonstrate that, after treatment with ibogaine or harmaline, a subset of Purkinje cells

in the vermis degenerates. We observed a loss of the neuronal proteins microtubule-associated protein 2 and calbindin co-extensive with loss of Nissl-stained Purkinje cell bodies. Since these drugs produce sustained activation of inferior olivary neurons, we hypothesize that release of an excitatory amino acid from climbing fiber synaptic terminals may lead to excitotoxic degeneration of Purkinje cells. [Degeneration of Purkinje cells in parasagittal zones of the cerebellar vermis after treatment with ibogaine or harmaline O'Hearn E et al, 1993]

The pyridine derivative 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is recognized as a crucial neurotoxin which destroys nigrostriatal dopamine cells, thereby inducing neurological signs relevant to idiopathic Parkinson's disease. In the present study, we have revealed MPTP neurotoxicity to cerebellar Purkinje cells in mice. Systemic MPTP injections to mice resulted in a substantial loss of Purkinje cells in a dose-dependent fashion. The MPTP-induced Purkinje cell loss occurred markedly in the crus I and II ansiform lobules and the paraflocculus. Such a neurotoxic effect was largely prevented by the monoamine oxidase B inhibitors pargyline and deprenyl, and the dopamine uptake inhibitors mazindol and benztropine. [MPTP neurotoxicity to cerebellar Purkinje cells in mice. Takada et al 1993]

Volkensin, a highly toxic protein retrogradely transported through axons, was used to target primary neuronal death in brainstem precerebellar relays after injection in the cerebellar cortex of rats. The reaction of astrocytes and microglia was studied with immunohistochemistry in the inferior olivary and pontine nuclei from 6 h to 14 days. Neurodegenerative features were evident since the first hours, especially in the pontine nuclei, and neuronal loss reached a plateau at 7 days in the inferior olive and at 10 days in the pons. Astrocytic activation, revealed by glial fibrillary acidic protein immunoreactivity, was concomitant with early signs of neuronal death and gradually increased. Microglia activation, revealed by OX-42 immunoreactivity, was evident at 2 days and became rapidly intense in precerebellar relays. At 1 week, marked ED-1 immunoreactivity also revealed phagocytic features of microglia, which persisted during the second week. In addition, major histocompatibility complex antigens (MHC) class I and II were induced in cells exhibiting microglial features. In the inferior olive, MHC I immunoreactivity was evident since 4 days and persisted at 14 days, whereas MHC II induction was intense at 7 days and subsided at 2 weeks. In the pontine nuclei high expression of both MHC antigens persisted instead at 14 days, probably reflecting the progression of neuronal death. Thus, targeted lethal injury of central neurons elicited prompt activation of both astrocytes and microglia; the marked microglia activation resulted in phagocytic features and immunophenotypic changes, with a temporal regulation that paralleled the evolution of neurodegenerative phenomena. [Glial reaction to volkensin-induced selective degeneration of central neurons. Cevolani et al 1990]

Mechanisms of Neuronal Injury; Excitotoxicity; Purkinje Cell Degeneration; Neurodegenerative Diseases: Spinocerebellar Ataxias  
We are interested in mechanisms of excitotoxic neuronal injury and in developing methods for neuroprotective intervention. Purkinje cells are integrative neurons of the cerebellar cortex and are highly susceptible to a variety of insults, both experimental and clinical. The explanation for the heightened susceptibility of these neurons remains uncertain. We have developed an in vivo animal model of Purkinje cell degeneration in which neurotoxic alkaloids, including ibogaine and harmaline, cause prolonged activation of inferior olive neurons that results in trans-synaptic, excitotoxic degeneration of Purkinje cells. Climbing fiber axons from inferior olive neurons are glutamatergic and innervate Purkinje cells in a uniquely dense fashion, a factor which may underlie the susceptibility of Purkinje cells to injury. Through pharmacologic modulation of drug-induced Purkinje cell degeneration we are focusing on the contribution of specific glutamate receptor subtypes and on signal transduction mechanisms that lead to Purkinje cell death. Identification of neuronal events in this injury cascade may provide therapeutic targets to ameliorate neuronal damage. An associated interest is in relating mechanisms of neuronal injury to clinical neurologic disease in human patients. In collaboration with Russell Margolis and Christopher Ross at Johns Hopkins, we are evaluating patients with neurodegenerative conditions affecting the cerebellum, e.g., the spinocerebellar ataxias. Our goals include relating genetic abnormalities, such as expanded trinucleotide repeats, to cellular mechanisms that result in neuronal degeneration.

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### **Other disorders of Cerebellar degeneration**

1. Primary degeneration of the granular layer of the cerebellum is an autosomal recessive disorder exhibiting characteristic features: hypotonia, strabismus, delayed motor development, nonprogressive ataxia, delayed language development with dysarthria and mental retardation. [Primary degeneration of the granular layer of the cerebellum. A study of 14 patients and review of the literature. Pascual Castroviejo et al; 1994]
2. The period of rapid brain growth that occurs relatively late in development has been shown to be vulnerable to alcohol-induced brain growth deficits and neuron loss in rats using repeated daily exposure to alcohol. Exposure to high peak BACs, even for a relatively short period during the brain growth spurt, constitutes a substantial risk to the developing brain, and even a moderate exposure may result in loss of more vulnerable neurons. [A single day of alcohol exposure during the brain growth spurt induces brain weight restriction and cerebellar Purkinje cell loss. Goodlett CR et al; 1990]
3. The cerebellar cortex in patients with autosomal dominant and recessive ataxia was studied by Golgi impregnation and immunocytochemistry in order to gain further insight into the pathogenesis of neuronal atrophy which accompanies these disorders. Purkinje cell atrophy progressed from loss and simplification of the dendritic tree to disappearance of the cell body. While these cells appeared to be especially vulnerable, other neurons of the molecular and granular layers were not exempt. There was evidence that at least some extracerebellar afferents, such as mossy fibers, were also affected by the disease process. [The Purkinje cell and its afferents in human hereditary ataxia. Koeppen Ahl; 1991]
4. We studied the nervous systems and tumors of two patients with anti-Yo-associated paraneoplastic cerebellar degeneration (PCD). In both patients the underlying tumor was an ovarian adenocarcinoma that expressed Yo antigens and contained extensive infiltrates of lymphocytes and plasma cells. The major central nervous system findings were a complete loss of cerebellar Purkinje cells with Bergmann astrogliosis. [Inflammatory infiltrates and complete absence of Purkinje cells in anti-Yo-associated paraneoplastic cerebellar degeneration. Verschuuren J etal; 1996]

### **Characteristics of Cerebellar dysfunction**

**a. Disequilibrium** - Falling: forward, backward, laterally when standing; unsteady, staggering gait; sensations of spinning and nausea.

**b. Muscle tone disturbance** - Softness of muscle bellies on palpation; decreased tendon reflexes; asthenia (muscles tire easily). Pendular swinging of dependent limb segment after displacement.

#### **c. Movement disorders:**

I. Incoordination of movements - Ataxia, asynergia - decreased capability for smooth, cooperative, segmental action between a series of muscle groups.

II. Decomposition of movements - Complex movement performed as a sequence of irregular disjointed episodes.

III. Adiadochokinesis - Inability to rapidly pronate and supinate.

IV. Dysmetria - Inability to correctly judge distances. Tested by reaching out and touching an object ("prepointing; pastpointing")

V. Inability to trace a specific course with finger or heel (e.g., right heel to left knee).

VI. Staggering gait - Tendency to fall, particularly with closed eyes.

VII. Intention tremor - Tremor when voluntary movement is attempted.

**d. Speech deficits** - Slow onset, slurring, jerky, intermittent sound productions with explosive nature: "scanning speech".

**e. Cerebellar nystagmus** - Inability to fixate on object. Conjugate drift of eyes away from it, with rapid return. May be positional (more pronounced when body adopts a particular posture), or directional (increasing when subject attempts to gaze in particular direction).

### **Additional References**

1. Microtubule-associated protein 1C (MAP 1C) is now defined as brain cytoplasmic dynein. Dynein is localized in purkinje cells of cerebellum and axons of central and peripheral nervous systems. Yoshida T. et al; 1992
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3. Development of the brainstem and cerebellum in autistic children; Hashimoto T. et al; Dept. of Ped., Univ. of Tokushima Sch. of Med.; *No To Hattatsu* 1994
4. Glutaredoxin protects cerebellar granule neurons from dopamine-induced apoptosis by dual activation of the ras-phosphoinositide 3-kinase and jun n-terminal kinase pathways. Daily D. et al , Dept. of Neurobiochemistry, George S. Wise Faculty of Life Sciences, Tel Aviv Univ., Ramat Aviv, Tel Aviv, Israel. *J Biol Chem* 2001