CHAPTER 20
Motor System III: Cerebellum and Movement

ANATOMIC CONSIDERATIONS

Subdivisions of the Cerebellum

A number of schemes for dividing the cerebellum into various lobes and lobules have been devised. From a functional standpoint, it is perhaps best for the student to visualize the cerebellum as composed of various longitudinal and transverse divisions. In order to visualize these subdivisions, it is necessary to unfold and to flatten the cerebellum as shown in *Figure 20-1.*

Longitudinal Divisions

The major longitudinal divisions are the median (vermal cortex), the paramedian (paravermal), and lateral (remainder of the cerebellar hemispheres).

The major projections and functional correlations are outline in Table 20-1. In general, the median (vermal) region is concerned with the medial descending systems and with axial control. The lateral and paramedian regions are concerned with the lateral descending systems and with the appendages (the limbs) (midline to axis; lateral to appendages).

Transverse Divisions

TABLE 20-1 LONGITUDINAL SUBDIVISIONS OF THE CEREBELLUM

Median	Paramedian	Lateral
(Vermal Cortex)	(Paravermal)	(Remainder of cerebellar hemisphere)
Projects to:	**Projects to:**	**Projects to:**
Fastigial nucleus (globus and emboliform)	Interpositus nuclei	Dentate nucleus lateral
Role in:	**Role in:**	**Role in:**
Posture & move-movements of body (axial)	Discrete ipsilateral extremity movements (appendicular)	Discrete ipsilateral extremity patterns of movement. Coordinated with cerebral cortex, thalamus, and red nucleus. Initiating, planning and timing of movements.

The transverse subdivisions are essentially phylogenetic divisions.

(1) The archicerebellum is composed of a

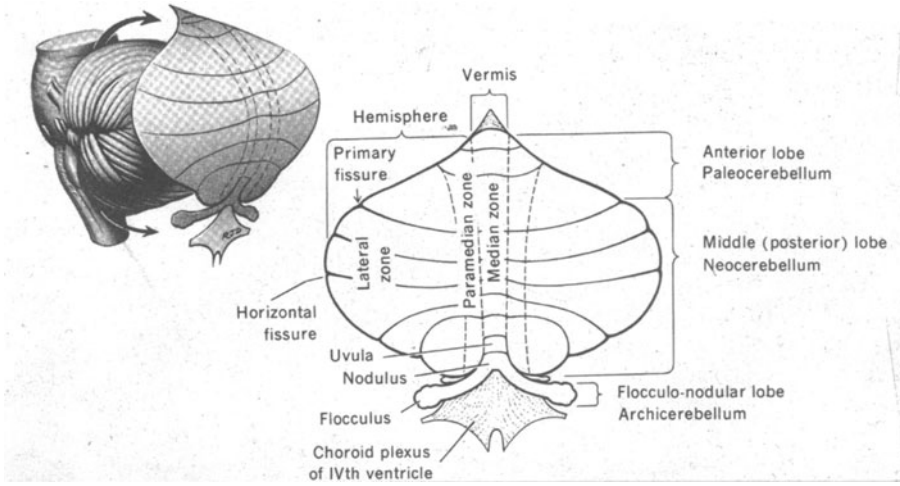

Figure 20-1. Major transverse and longitudinal subdivisions of the cerebellum. The surface has been unfolded and laid out flat. (From Noback, C.R. et al: 1991. The Human Nervous System. 4th edition, Philadelphia. Lea & Febiger p. 282.

flocculus and nodulus and is related primarily to the vestibular nerve and vestibular nuclei. Reflecting this anatomical relation, the archicerebellum has a role in control of equilibrium (balance), axial posture, and eye movement.

(2) The paleocerebellum, or anterior lobe, relates primarily to the spinocerebellar system and to its analogue for the upper extremities, the cuneocerebellar pathway (the lateral cuneate nucleus is the analogue of the dorsal nucleus of Clarke). Its major function, however, appears more related to the lower extremities than to the upper extremities. The primary fissure separates the anterior lobe from the middle posterior lobe.

(3) The middle, or posterior, lobe, the neocerebellum, relates primarily to the neocortex. The function of the neocerebellum is primarily the coordination of discrete movements of the upper and lower extremities (see Table 20-2) Transverse Divisions of the Cerebellum

CYTOARCHITECTURE OF THE CEREBELLUM

In contrast to the cerebral cortex, all areas of the cerebellar cortex are relatively thin and have the same basic three-layered cytoarchitectural pattern, consisting of an outer molecular layer, a Purkinje cell layer and an inner granule cell layer with an underlying medullary layer of white matter. The arrangement of cells and the basic synaptic connections are indicated in *Figure 20-2.* The arrangement of cells and the basic synaptic connections are indicated in *Figure 20-3.* Afferent fibers enter the cerebellar cortex as *mossy fibers.* These fibers are so named because each terminates in a series of moss-like glomeruli, where axodendritic synaptic contacts are made with granule cells. The mossy fibers have already been encountered as spinocerebellar, cuneocerebellar, corticopontocerebellar, vestibulocerebellar, or reticulocerebellar pathways.

The granule-cell axon is sent into the molecular layer where it divides into two long branches. These branches travel parallel to the long axis of the cerebellar folium and are designated as *parallel fibers.* These fibers make excitatory synaptic contact with the extensive dendritic arborizations of Purkinje cells, as well as with stellate cells, Golgi cells, and basket cells. The basket cells inhibit the Purkinje cells via axosomatic synapses as these projections are inhibitory in nature The outflow of the Purkinje cells is inhibitory in nature The tar-

TABLE 20-2 TRANSVERSE DIVISIONS OF THE CEREBELLUM

Archicerebellum (Floccular nodular lobe)	Paleocerebellum Anterior Lobe	Neocerebellum (Middle, or posterior, lobe)
CONNECTIONS: Vestibular	CONNECTIONS: Spinocerebellar & Cuneocerebellar & spino-olivary (inferior olive)	CONNECTIONS: Neocortex
ROLE: Axial equilibrium (Trunk primarily) Posture, Muscle tone, Vestibular reflexes, Eye movements	ROLE: Equilibrium Posture Muscle tone in lower extremities Coordinated movements lower extremities eg. heel to shin	ROLE: Limb coordination in phasic posture movements (upper and lower extremities) Possible role in higher executive functions and emotion

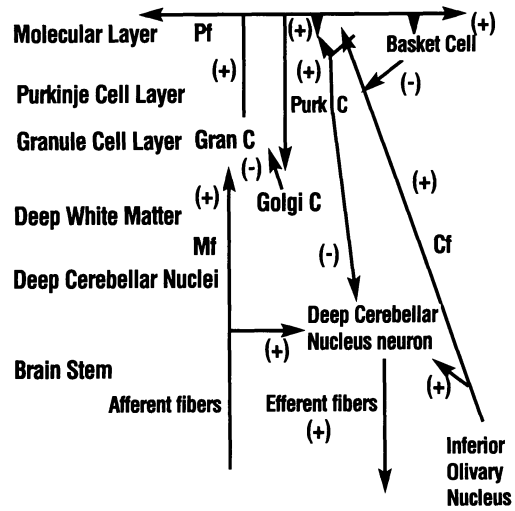

Figure 20-2. The most significant cells, connections, the afferent and efferent fibers in the cerebellar cortex. . Arrows show direction of axonal conduction. (+) = excitatory ;(-) = inhibitory. Cf= climbing fibers; pf = parallel fiber; mf = mossy fiber . Refer to text.

get of the axons of the Purkinje cells is the neurons of the deep cerebellar nuclei. The axons of the neurons in these deep cerebellar nuclei are the major outflow from the cerebellum to the brain stem and thalamus.

Several additional systems must be considered. The *climbing fibers* are excitatory to the Purkinje-cell dendrites. These fibers originate in the contralateral inferior olivary nuclei and represent a long-term latency pathway from the spinal cord or cerebral cortex to the cerebellum (olivocerebellar). These fibers are so named because they climb and wrap around the dendrites and body of the Purkinje-cell neurons, making several hundred synaptic contacts. Stimulation of a single climbing fiber results in large postsynaptic potentials and in large high-frequency bursts of discharges.

The parallel fibers also have excitatory synapses in the molecular layer, but they synapse with the dendrites of the Golgi cells. The Golgi cell, in turn, is inhibitory to the granule cell with a synapse within areas of the molecular layer referred to as glomeruli. The parallel fibers also excite other interneurons (small stellate cells) in the molecular layer, which, in turn, are inhibitory to the dendrites of Purkinje cells.

GABA (gamma aminobutyric acid) is the inhibitory transmitter for the Purkinje, basket, stellate, and Golgi cells. Since the outflow from the cerebellar cortex occurs via the axons of Purkinje cells and since this outflow is inhibitory to the deep cerebellar nuclei, it is logical to ask what excitatory influences drive the neurons of these deep nuclei. The answer is that collaterals of the mossy fibers and climbing fibers serve this function.[1]

AFFERENTS

The inputs to the cerebellum may be summarized as follow:

A. Via the inferior cerebellar peduncle (restiform body):

1. Uncrossed dorsal spinocerebellar and cuneocerebellar

2. Crossed olivocerebellar

3. Uncrossed reticulocerebellar (from lateral reticular and paramedian nuclei)

B. Via the juxta-restiform body

1. Uncrossed from vestibular nuclei are predominantly to the floccular nodular lobe, the archicerebellum, and the midline vermis.

2. Uncrossed from vestibular nerve (note that some fibers from the vestibular nerve bypass the vestibular nuclei and enter the cerebellum directly)

C. Via the middle cerebellar peduncle (brachium pontis):

1. The corticopontocerebellar input (via the pontine nuclei) is primarily to the neocerebellum of the lateral hemisphere.This is crossed from the opposite cerebral hemisphere.

D. Via the superior cerebellar peduncle (brachium conjunctivum):

1. Crossed ventral spinocerebellar is primarily to the anterior lobe (paleocerebellum) and the intermediate area of the paraflocculus.

2. Tectal cerebellar

The superior cerebellar peduncle, then, serves only a minor role as afferent to the cerebellum. Its major role is as the efferent pathway.

EFFERENTS

A. Superior Cerebellar Peduncle (Brachium Conjunctivum).

1. Dentate nuclei and interpositus (globus and emboliform) nuclei, there is a major projection via the crossed brachium conjunctivum (superior cerebellar peduncle) to the ventral lateral (and ventral anterior) nucleus of the thalamus and to the red nucleus (dentatorubral-thalamic pathway).

2. Descending division of the brachium conjunctivum conveys impulses to the paramedian reticular nuclei.

B. Inferior Cerebellar Peduncle.

1. The archicerebellum projects directly from the floccular nodular lobe and via the fastigial nuclei to the vestibular (lateral vestibular nucleus) and reticular areas of the brain stem.

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[1]*However, the mossy fibers from the pontine and brain stem reticular nuclei apparently do not serve this collateral excitatory function.*

2. The fastigioreticular and fastigiovestibular pathways hook around the superior cerebellar peduncle as the uncinate fasciculus. In addition, impulses are also conveyed via the juxtarestiform body.

C. Middle Cerebellar Peduncle. This contains only afferent connections from the cerebrum via the pons into the neocerebellum.

TOPOGRAPHIC PATTERNS OF REPRESENTATION IN CEREBELLAR CORTEX

Stimulation of tactile receptors or of proprioceptors results in an evoked response in the cerebellar cortex. There is a topographic pattern of representation. Visual and auditory stimuli evoke responses primarily in the midline vermis. Stimulation of the specific areas of the cerebral cortex also evokes responses from the cerebellar cortex in an appropriate topographic manner. Moreover, direct stimulation of the cerebellar cortex in the decerebrate animal will produce, in a topographic manner, movement or changes in tone of flexors or extensors. The general pattern of representation is consistent with the patterns of sensory and cortical representation previously noted.

A possible pattern of somatotrophic representation in the primate cerebellum is shown in ***Figure 20-3.*** It is important to recall that there is no conscious perception of stimuli arriving at the cerebellar level.

Vestibular stimulation evokes responses not only in the floccular nodular regions but also in the superior and inferior midline vermis.

FUNCTIONS OF THE CEREBELLUM AND CORRELATIONS

The cerebellum acts as a servomechanism, that is, as a feedback loop that dampens movements and motor power to prevent overshoot and oscillation (that is, tremor). In short, it acts to maintain stability of movement and posture. More recently, a role in higher motor function, such as the initiation of planning, the timing of movement, and motor learning, has been suggested for the cerebellum.

REGIONAL FUNCTIONAL CORRELATIONS

We have already discussed the functional relation of the longitudinal and transverse subdivisions of the cerebellum. It is evident that these two classifications overlap from a functional correlation standpoint.

From a functional standpoint, we may specify the following correlations:

1. Vestibular Reflexes and Eye Movement

a. Anatomic Correlation: Floccular nodular lobe

b. Major Input: Vestibular labyrinth (semicircular canals and otolith organs)

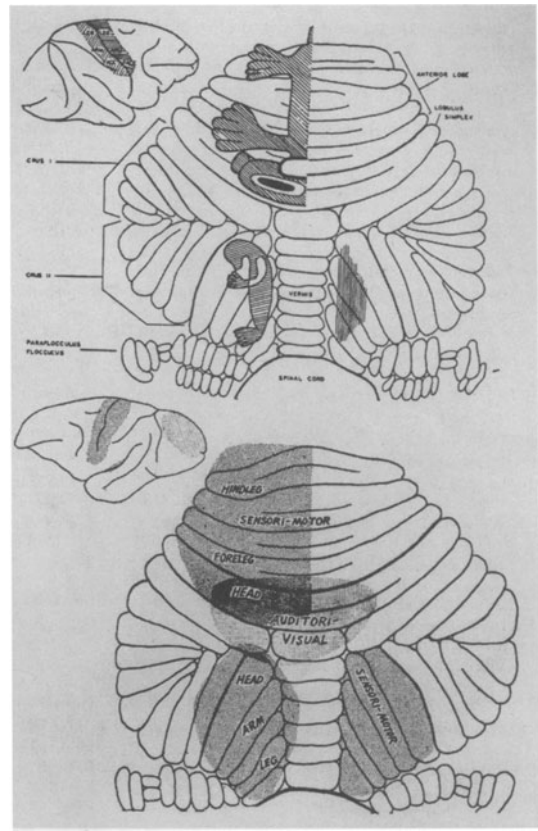

Figure 20-3: Topographic localization in cerebellum. A, Summary of projections from the sensory area and the motor area in the monkey; B, Summary of corticocerebellar projections in the monkey. Note that there is a unilateral representation on the dorsal surface and a representation within each paramedian lobule on the ventral surface. At the lateral margin the division between crus I and crus II is essentially the border between the dorsal and ventral surface. See Figure 20-1 for terminology in human cerebellum. From Snider. R.S.: 1950. Arch.Neurol.Psych. 64:204 (AMA).

c. Major Deep Nucleus: Vestibular nuclei (lateral)

d. Major Connections: Medial descending systems, vestibulospinal and medial longitudinal fasciculus and extraocular motor nuclei

2. Posture and Equilibrium of the Trunk

A. a. Anatomic Correlation: Floccular nodular lobe (vestibulocerebellum)

b. Major Input: Vestibular labyrinth as above

c. Major Deep Nucleus: Vestibular nuclei (lateral)

d. Major Connection: Medial descending systems - vestibulospinal systems (medial and lateral)

B. a. Anatomic Correlation: Midline vermis (spinocerebellum)

b. Major Inputs:

1. Vestibular labyrinth

2. Dorsal spinocerebellar and cuneocerebellar from body and proximal limbs

3. Trigeminal

4. Visual and auditory

c. Major Deep Nucleus: Fastigial

d. Major Connections: Medial descending motor systems:

1. Via juxtarestiform body and central tegmental system to pontine and medullary reticular nuclei (origin of medial and lateral reticulospinal tracts) and to vestibular nuclei (origin of vestibulospinal tracts).

2. Via superior cerebellar peduncle (decussated) to ventral nucleus of thalamus to motor cortex to anterior corticospinal tract

3. Distal Motor Control and Speech/ Voice Control

a. Anatomic Correlation: Intermediate lobe (paravermal or paramedian zone-spinocerebellum)

b. Major Input: Dorsal spinocerebellar and cuneocerebellar

c. Major Deep Nuclei: Interpositus (globose and emboliform)

d. Major Connections: Lateral descending motor system, superior cerebellar peduncle via decussation to magnocellular sector of the red nucleus (origin of rubrospinal system) and to ventral lateral nucleus of thalamus and from the thalamus to primary motor area and area 6 of supplementary motor cortex (origins of the crossed lateral corticospinal system)

3A. Speech

a. Anatomic Correlation: Superior paravermal area (more often left than right). Damage produces cerebellar dysarthria which affects prosody, harmony, and rhythm of speech rather than sequential or semantic aspects (see Amarenco et al, 1991; Lechtenberg and Gilman, 1978 for additional discussion).

4. Initiation, Planning and Timing of Movement

a. Anatomic Correlation: Lateral cerebellar hemisphere (cerebrocerebellum)

b. Major Input: Motor and premotor cerebral cortex (areas 4 and 6) and parietal cortex (areas 1, 2, 3, 5) to pontine nuclei to lateral neocerebellum (after decussation) via the middle cerebellar peduncle

c. Deep Nucleus: dentate

d. Major Connection: Via decussation of superior cerebellar peduncle to

1. Red nucleus (parvocellular) with subsequent rubro-olivary fibers

2. Ventral lateral nucleus of thalamus, then projecting to motor and premotor cerebral cortex. From these areas, as already discussed, originate the lateral descending systems lateral corticospinal and corticorubrospinal and lateral reticulospinal and the anterior corticospinal systems.

EFFECTS OF DISEASE ON THE CEREBELLUM

The cerebellum, may be viewed as a machine processing information from many sources (sensory receptors, vestibular nuclei, reticular formation, and cerebral cortex) and then acting to smooth out the resultant movements or postures. Sudden displacements or lurches are prevented. The large number of inhibitory feedback circuits in the cerebellum (the major influence of Purkinje cells on deep cerebellar nuclei being inhibitory) qualifies the cerebellum for this role. Lesions may then result in undamped oscillation. As a result,

tremor perpendicular to the line of movement may occur, called intention or action tremor. Lesions may also impair the ability to respond to sudden displacements, resulting in instability of posture and gait (ataxia). Release of function of ventral lateral nucleus of thalamus may also occur.

The cerebellum is not designed for the direct, fast-conduction control of movements. Thus, it is not surprising that, in the monkey, total ablation may produce little effect, although some deficit in contact placing may be evident. In humans, extensive destruction of cerebellum may be present with little obvious deficit. Moreover, cerebellar symptoms, if present in a "static" disease process (such as cerebrovascular accidents), often disappear with time. However, more specific tests may still reveal a minor deficit in speed and coordination.

More recent studies suggest a role for the cerebellum in classical conditioning and in motor learning particularly as regards the memory aspect for the timing of movements (Raymond et al, 1996). In addition, a role of the cerebellum in higher order cognitive and emotional functions has been suggested by the studies of Schmahmann&Sherman, 1998, Levinsohn et al, 2000,Riva&Giogi, 2000.In patients with lesions of the posterior lobe and vermis, there was an impairment of executive functions such as planning, set shifting, verbal fluency, abstract reasoning, working memory as well as visual spatial organization and memory. Higher language disturbances also occurred. In addition these patients had a personality change characterized by blunting of affect or disinhibition and inappropriate behavior. This cognitive and affective syndrome suggested a disruption of the modulatory effects of cerebellum on the prefrontal, posterior parietal and limbic circuits discussed in Chapter 18. These changes did not occur with lesions of the anterior lobe. The effects on cognitive and emotional function in patients with prenatal cerebellar hypoplasia may be even more serious and may include autism (Courchesne, et al, 1994,Allin et, al 2001)

MAJOR SYNDROMES:

While we will discuss three anatomically distinct syndromes of cerebellar disease (the floccular nodular lobe, the anterior lobe, and the lateral hemisphere) it should be pointed out that these strict anatomic borders do not confine many diseases that affect the cerebellum. Moreover, the cerebellum is positioned in a relatively tight compartment with bony walls and a relatively rigid tentorium cerebelli above. An expanding lesion in the posterior fossa, then, may produce a generalized compression of the cerebellum. In such clinical situations, it may be possible to differentiate only between midline (vermal) involvement and lateral (cerebellar hemisphere) involvement. Midline lesions produce disorders of equilibrium and axial ataxia; lateral and lateralized paramedian lesions produce appendicular ataxia and tremor.

SYNDROME OF THE FLOCCULAR NODULAR LOBE AND OTHER MIDLINE CEREBELLAR TUMORS

The major findings in the human, monkey, cat and dog are a loss of equilibrium and an ataxia (unsteadiness) of trunk, gait, and station. Thus, the patient, when standing on a narrow base with eyes open, has a tendency to fall forward, backward, or to one side. The patient may be unable to sit or stand. The patient walks on a broad base, often reeling from side to side, and often falling. Despite the loss of equilibrium, the patient usually does not complain of a rotational vertigo. When recumbent in bed, the patient often fails to show any ataxia or tremor of limbs. Thus, the finger-to-nose and heel-to-shin tests are performed without difficulty. With unilateral disease of the floccular nodular lobe, a head tilt may be present. In addition, spontaneous horizontal nystagmus may be present as a transitory phenomenon.

In humans, the most common cause of this syndrome is neoplastic. The type of neoplasm depends on the age of the patient. The most likely cause in an infant or child[2] is a medulloblastoma, a tumor arising in nests of external granular cells in the nodulus forming the roof of the 4th ventricle. In older children and

young adults, the ependymoma, a tumor arising from ependymal cells in the floor of the fourth ventricle, may cause this syndrome by pressing upward against the nodulus. In adults it is more appropriate to speak of midline tumors of the vermis since the tumors do not selectively involve the floccular nodular region. In middle-aged adults, the most common cause is probably the midline hemangioblastoma. In older adults, metastatic tumors may produce this syndrome. At all ages, rare arteriovenous malformations may produce the syndrome.[3]

The course of a medulloblastoma is indicated in the following case history:

Case 20-1: This 27-month old white female had been unsteady in gait, with poor balance, falling frequently since the age of 13 months, when she began to walk. Three months prior to admission, in relation to a viral infection manifested by fever and diarrhea, the patient developed increasing anorexia and lethargy. One-month prior to admission, vomiting increased, and the patient also became more irritable. Perinatal history had been normal, and head circumference had remained normal.

Neurologic examination: *Mental Status:* The child was irritable but cooperative. *Cranial Nerves:* The fundi could not be visualized. Bobbing of the head was present in the sitting position. *Motor System:* A significant ataxia of the trunk was present when sitting or standing. Gait was broad-based and ataxic, requiring assistance. No ataxia or tremor of the extremities was present.

Clinical diagnosis: Probable midline cerebellar tumor, most likely based on age a medulloblastoma

Laboratory Data: *Air-contrast ventriculogram* demonstrated the fourth ventricle was deformed by a mass arising from the nodulus of the cerebellum. There was secondary enlargement of the lateral and third ventricles and marked forward displacement of the cerebral aqueduct.

Hospital Course: Doctor Peter Carney performed a suboccipital craniotomy, which confirmed the presence of a medulloblastoma with many malignant cells present in the cerebrospinal fluid obtained at surgery. Radiation therapy to the entire central nervous axis was begun one week after surgery. There was initial improvement but the patient deteriorated three months after the surgery and expired one month later despite chemotherapy .The findings at autopsy are demonstrated in *Fig. 20-4.*

At present, recommended therapy includes wide resection followed by radiotherapy to the entire CNS axis. Dissemination of tumor cells throughout the cerebrospinal fluid is frequent, because of the friable, cellular, non-stromal nature of the lesion. At present, 5-year survival has been increased to 60%. Recurrences may be treated with chemotherapy although the combination of radiotherapy and chemotherapy may produce significant pathologic alterations in white matter. Refer to Chapter 13 and 27 for additional discussion.

Mid line cerebellar tumor in the adult: the following case 20-2 presents an example of a midline cerebellar tumor metastatic from breast with primary symptoms of gait ataxia, headache, vertigo and vomiting.

Case 20-2: This 67-year-old white female 6 weeks prior to admission developed intermittent vertigo and then two weeks prior to admission a progressive ataxia of gait followed by headaches and vomiting. Past history: This patient had a poorly differentiated highly malignant infiltrating ductal adenocarcinoma of the left breast for which she had undergone lumpectomy 6 years; and a radical mastectomy followed by radiation therapy, 3 years prior to admission.

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[2] *Medulloblastomas may occasionally occur in adolescents and young adults.*

[3] *Progressive multiple sclerosis may produce in the young or middle-aged adult severe involvement of white matter in the cerebellum and brain stem, resulting in severe truncal ataxia, in which the patient is ataxic in both the sitting and standing positions. Such cases almost always also manifest severe appendicular involvement, that is, the cerebellar syndrome is not selective.*

Neurological examination (in the emergency room): *Cranial Nerves:* There was an absence of venous pulsations on funduscopic examination suggesting a mild increase in intracranial pressure. *Motor System:* She had difficulty standing tending to fall to the right. She was unable to walk because of severe ataxia. There was no limb dysmetria. *Reflexes:* The right plantar response was equivocal.

Clinical diagnosis: Midline cerebellar tumor metastatic from breast.

Laboratory data: *CT scan* demonstrated a large (3-4 cm) enhancing tumor was present involving the midline vermis and right paramedian cerebellum and compressing the fourth ventricle subsequently confirmed by *MRI scans* of the brain *(Fig.20-5). CT scan of abdomen* demonstrated two possible metastatic lesions in the liver.

Subsequent course: The patient received dexamethasone with significant improvement within 12 hours. At the insistence of the patient, Dr. Gerald McGullicuddy resected the solitary central nervous system metastatic lesion. Following surgery she received 3000cGy(rads) whole brain radiation and was begun on the antitumor agent tamoxifen. She expired at home, four months after surgery of systemic complications of the malignancy.

SYNDROME OF THE ANTERIOR LOBE:

Stimulation or ablation of the anterior lobe in the cat or dog may produce significant changes in muscle tone. Thus, stimulation of the middle anterior lobe results in a decrease in spindle discharge and inhibits gamma rigidity of the decerebrate preparation. Stimulation of the intermediate area of the anterior lobe produces an increased spindle discharge and facilitates gamma rigidity in the decerebrate preparation. Actual ablation of the anterior lobe in these animals or functional ablation (cooling) produces an increase in decerebrate rigidity without a change in the gamma system (alpha rigidity). However, in humans, ablation of the anterior lobe does not change tone.[4] The major symptoms are an ataxia of gait with a marked side-to-side ataxia of the lower extremities as tested in the heel-to-shin test. The upper extremities, in contrast, are affected to only a minor degree.

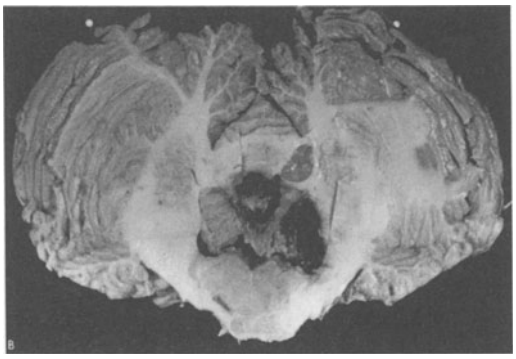


Figure 20-4. Medulloblastoma: Syndrome of the flocculonodular lobe: Case 20-1. Vomiting and truncal ataxia were present without tremor or ataxia of the extremities. (Courtesy of Dr. John Hills). Refer to text.

This area corresponds to the representation of the lower extremities and to the area of projection of the spinocerebellar pathways.

Typical of this syndrome are cases of alcoholic cerebellar degeneration ***(Figure 20-6),*** where a severe loss of Purkinje cells occurs in the anterior lobe. Although this degeneration occurs primarily in alcoholics, the basic etiology may be a nutritional deficiency (the specific factor is most likely thiamine).

The major findings of a broad-based, staggering gait with truncal ataxia and heel-to-shin ataxia can be related to the anterior lobe of the cerebellum. Since symptoms improve or do not progress after the discontinuation of alcohol, and the administration of multiple B vitamins, a toxic or nutritional factor may be postulated. (The reliability of the history of alcohol intake is always open to question. The amount stated by the patient is usually assumed to be the minimum amount.) Note that a similar acute cerebellar syndrome occurs as one aspect of the Wernicke-Korsakoff's syndrome (refer to Chapter 30). At the present time, the diagnosis of cerebellar atrophy may be confirmed by MRI (midline sagittal section) or by CT scan. As a result, evidence of cerebellar atrophy is now found in many patients presenting with other aspects of chronic alcoholism or other nutritional disease who do not

necessarily present with initial symptoms of ataxia.

Case 20-3 presented on the CD-ROM illustrates alcoholic cerebellar degeneration.

In other cases, this syndrome is the result of a chronic degenerative disease with a genetic basis. As in alcoholic cerebellar degeneration, the predominant histologic change is the loss of Purkinje cells in the anterior lobe. In contrast to alcoholic cerebellar degeneration, the pathology is usually more widespread and not strictly limited to the anterior lobe. In the following case history, the major involvement was primarily of the anterior lobe. There was definite family history, including evidence of consanguinity.

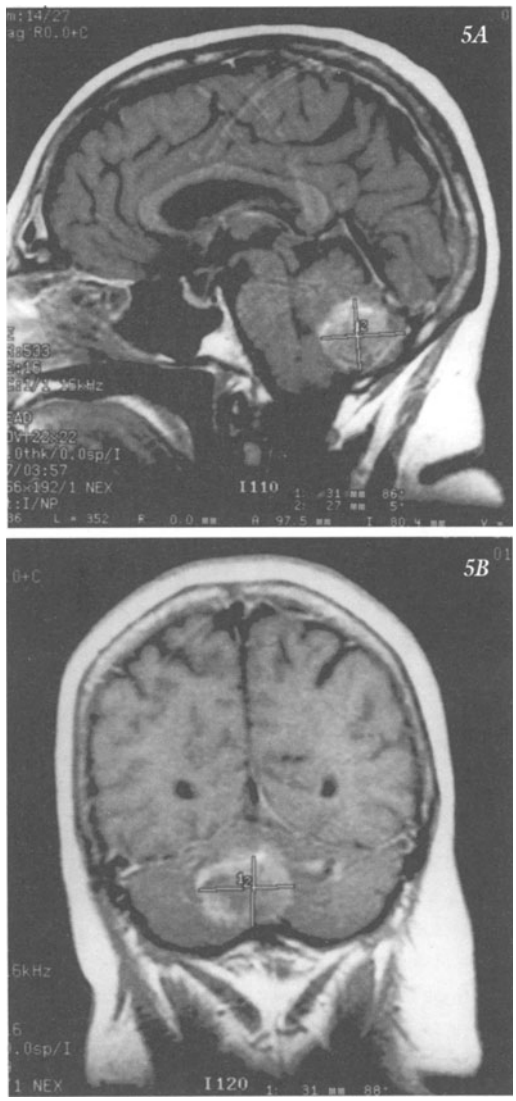


Figure 20-5. Metastatic midline cerebellar tumor: Case 20-2 .MRI (TI) a) sagittal section b) coronal section. Refer to text.

Case 20-4: A 45-year-old single white male carpenter presented with a 4-year history of progressive unsteadiness in walking, present during the daytime as well as at night and a minimal loss of coordinated movements in his hands. He felt that his greatest deficit was unsteadiness. He had some numbness at the toes and minor difficulty in swallowing. His mother and father were second cousins. Several aunts and uncles had "trouble with their legs" in later life, resulting in a difficulty in walking.

Neurologic examination: *Cranial Nerves:* Intact except for minimal dysarthria. Horizontal nystagmus was present on lateral gaze, vertical nystagmus on upward gaze. *Motor System:* The patient walked on a broad base with an ataxia of trunk, as though intoxicated, reeling from side to side, with marked unsteadiness on turns. He was unable to walk a tandem gait with eyes open. A mild intention tremor was present, and there was minimal disorganization of alternating movements. In contrast a marked ataxia and tremor were evident on heel-to-shin test. *Reflexes:* There was a relative decrease in ankle jerks compared to knee jerks. *Sensory System:* There was a minimal decrease in vibration sensation at the toes.

Clinical diagnosis: Hereditary cerebellar degeneration involving predominantly anterior lobe

Laboratory Data: *Pneumoencephalogram* performed at the University of Virginia Hospital (Doctor Stewart) confirmed the significant atrophy of cerebellum.

OTHER CAUSES OF CEREBELLAR ATROPHY:

Prolonged high fever, meningitis, a post-

[4] *In general chronic lesions of cerebellum in humans do not alter tone or tendon reflexes. Acute lesions of cerebellum resulting from hemorrhage or surgery may produce transient hypotonia (Diener and Dichgans, 1992).*

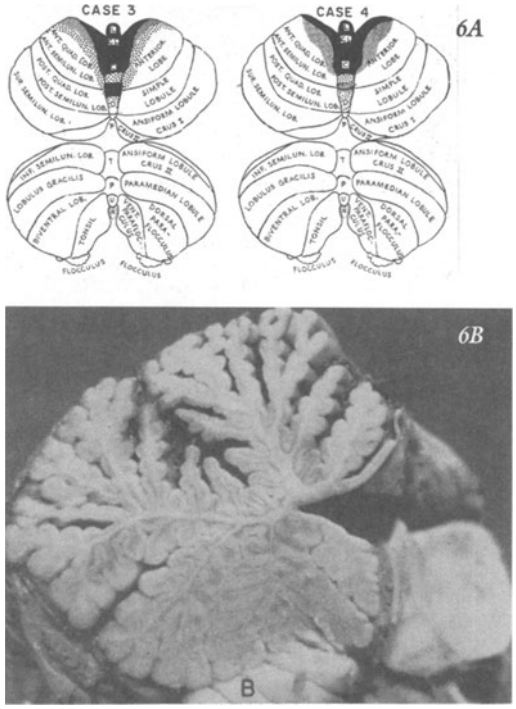


Figure 20-.6 Alcoholic cerebellar degeneration: The anterior lobe syndrome. There is a loss of Purkinje cells with atrophy of the cerebellar folia with relatively selective involvement of the anterior lobe: A) schematic representation of the neuronal loss, B) Atrophy of the anterior superior vermis in sagittal section. From Victor, M., R.D.Adams, and E.L.Mancall: 1959. Arch.Neurol. 1:579, 599, 600 (AMA).

infectious syndrome, and repeated grand mal seizures may all be associated with the development of an ataxia that suggests major involvement of the anterior superior vermis. In some of these cases, there is found on CT or MRI more widespread atrophy. At times, as in the case presented in *Figure 20-7*, other residual neurologic findings may also be present. The topography of cerebellar atrophy, particularly as regards midline structures, can best be studied with MRI. *Figure 20-8* demonstrates the findings in a patient with gait ataxia following high fever and meningitis, in which atrophy, although widespread, was most prominent in the anterior superior vermis.

When the ataxia is of acute or subacute onset in childhood, the possibility of a cerebellitis must be considered. A varicella or other viral infection often precedes this entity. Mononuclear cells may be present in cerebrospinal fluid. Whether this is a direct viral infection or a post-infectious entity remains unclear. . The major involvement is of the trunk although tremors of the head, trunk and limbs are also present. Recovery usually occurs over 6 months but occasionally recovery is incomplete.

Diener and Dichgans (1992) discuss the localization of ataxia of standing body posture. Their conclusions are as follows:

1. Lesions of the spinocerebellar portion of the anterior lobe (mainly observed in chronic alcoholics) result in body sway along the anterior/posterior axis with a frequency of 3 per second. This sway, or tremor, is provoked by eye closure. Visual stabilization of posture occurs. Since the direction of sway of the trunk is opposite that of the head and legs, the center of gravity is only minimally shifted and the patient does not fall.

2. In contrast, the lesions of the vestibulocerebellum (floccular nodular lobe and lower vermis), which are primarily mass lesions, produce a postural instability of head and trunk during sitting, standing, and walking. Postural sway occurs in all directions often at a frequency of less than 1 per second. Visual stabilization is limited; falls, therefore, are more frequent.

3. Spinal ataxia (as in tabes dorsalis and combined system disease) results predominantly in lateral body sway. Visual stabilization is prominent (positive Romberg test).

SYNDROME OF THE LATERAL CEREBELLAR HEMISPHERES (NEOCEREBELLAR OR MIDDLE-POSTERIOR LOBE SYNDROME):

A number of disease entities may produce symptoms that can be related to the lateral hemisphere. Some of these disease entities are mass lesions such as metastatic tumors *(Fig. 20-9)* or intrinsic tumors *(Figure 20-10)*. The diagnostic problem, moreover, is complicated by the fact that involvement of the cerebellar peduncles may produce many of the same symptoms that result from direct involvement of the cerebellar hemisphere. The student will

recall that the lateral medullary infarct produces an ipsilateral intention tremor and an impairment of alternating movements of the ipsilateral upper extremity. Occlusion of the posterior inferior cerebellar artery may produce an infarct of the lateral medulla and/or of the posterior inferior cerebellum as demonstrated in *Figure 13-12.*

Demyelinating disease, that is multiple sclerosis, may involve in a specific case, both the brain stem and cerebellum in a multifocal manner.

Cases presenting relatively pure focal involvement of the lateral hemisphere are those patients surviving after gunshot or shrapnel wounds. Such cases have been studied by Holmes (1939); they are not encountered frequently in civilian practice. Diener and Dichgans (1992) provide a more detailed physiologic analysis of lateral cerebellar lesions affecting the limbs.

The major findings in lateral hemisphere lesions, are the following signs and symptoms in the ipsilateral extremities: intention tremor, disorganization of alternating movements (dysdiadochokinesia), dysmetria, ataxia, and overshoot on rebound. The intention tremor may be described as a tremor perpendicular to the line of motion; often becoming more prominent on slower movements and as the target is approached.[5] This intention tremor may be noted in the finger-to-nose test. One may also demonstrate a similar tremor in the lower extremities as the patient attempts to

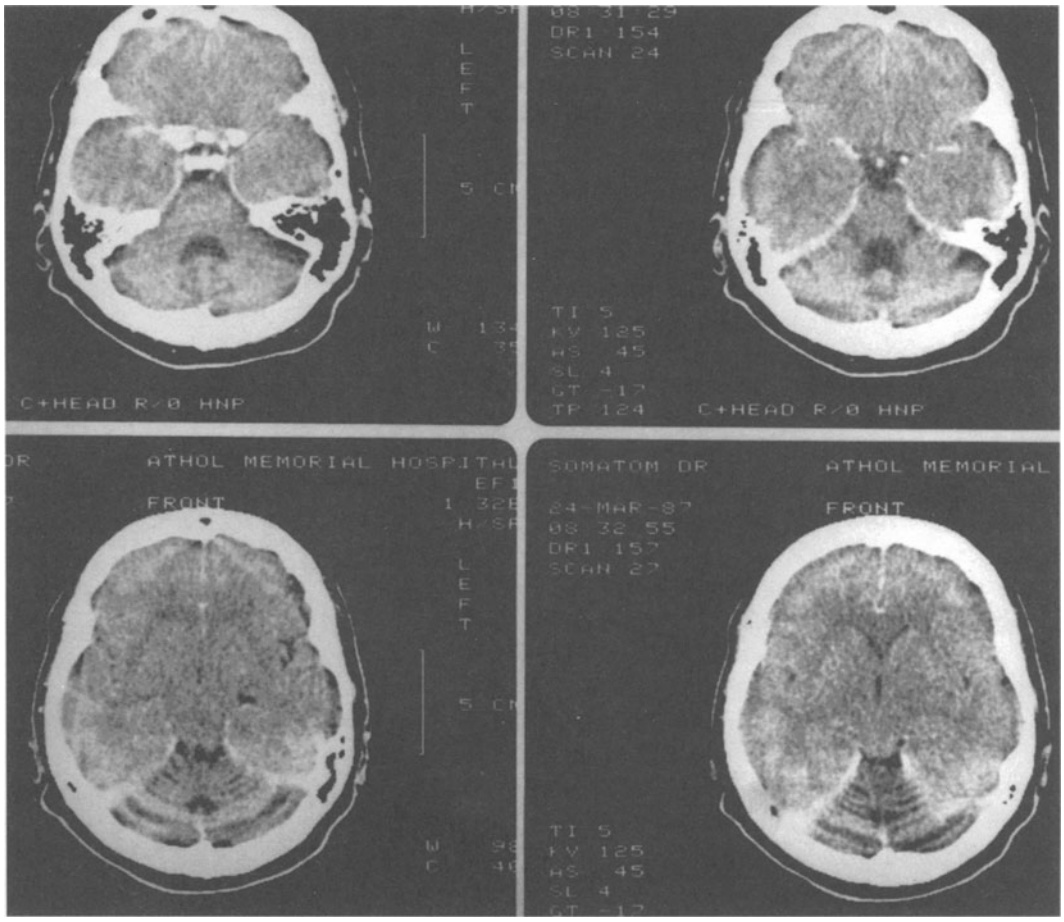


Figure 20-7: Generalized cerebellar atrophy most severe in the anterior superior vermis: CT scan. This 48-year-old female following an acute febrile illness and 3 weeks of coma at age 3 years, developed severe ataxia of stance and gait, with dysmetria on heel-to-shin testing, distal weakness in lower extremities and bilateral Babinski's signs.

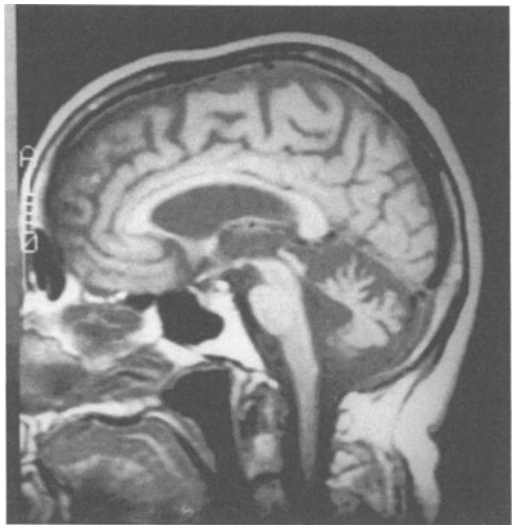


Figure 20-8:Cerebellar atrophy most prominent in anterior superior vermis with predominant anterior lobe syndrome: MRI. This 70-year-old female 23 years previously had prolonged markedly elevated temperature related to meningitis, coma and convulsions with a residual ataxia of stance and gait.

raise the foot off the bed to touch the examiner's finger or in the heel-to-shin test. As with the other signs of cerebellar disease, intention tremor is usually ipsilateral to the hemisphere involved.

At times, in addition to an intention tremor, a sustained postural "tremor" may be evident, more particularly if the superior cerebellar peduncle or its midbrain connections are involved. Brief jerks at the onset of movement (intention myoclonus) may occur when the dentate nucleus or superior cerebellar peduncle is involved.

The intention tremor represents a defect in the ability to dampen oscillations and to dampen overshoot. In the monkey, cerebellar tremor occurs despite deafferentation (section of the dorsal roots), a finding consistent with the concept that there is a central generator of oscillations. (However, other theories reviewed by Diener and Dichgans (1992) suggest the oscillations arise from dysfunction in long-latency transcortical reflexes.)

Having the patient slap the thigh above the knee with the hand at particular rhythm tests repetitive movements. One can also test for

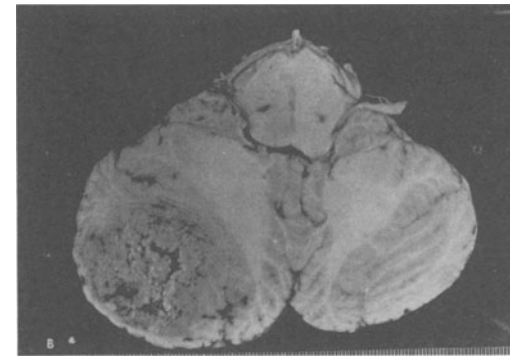


Figure 20-9. Lateral cerebellar syndrome. This patient with bronchiogenic carcinoma had nystagmus and appendicular ataxia .He had this major tumor in the lateral cerebellum and minor metastatic lesions in the cerebral hemispheres. (Courtesy of Dr. John Hills and Dr. Jose Segarra).

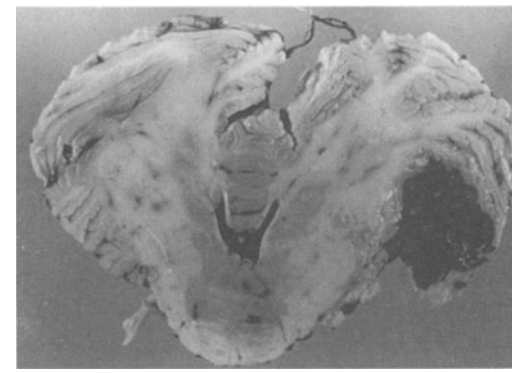


Figure 20-10. Syndrome of the lateral hemisphere: hemangioblastoma of cerebellum. This 72-year-old male had a 2-year history of vertex headache (worse on coughing), blurring of vision, diplopia, papilledema and a lateralized ipsilateral tremor on finger-to-nose testing. (Courtesy of Doctor Jose Segarra).

repetitive movement in the lower extremities by having the patient tap toes or heel on the floor. Alternating movements are tested by having the patient slap the hand on the thigh or on the opposite hand, alternating between the palmar and dorsal surface of the hand. In disease of the cerebellar hemisphere a marked disorganization of repetitive and alternating movement occurs. This is almost always ipsilateral to the hemisphere involved.

These patients are also said to demonstrate dysmetria. This may be defined as a defect in the estimation of the force and rate of movement necessary for an extremity to reach a tar-

get. The result in the finger-to-nose test is that the patient fails to accurately touch the finger to the nose. The finger may overshoot its goal or fail to reach the goal. Note that in disease involving the older regions of cerebellum, eye movements may also be described as dysmetric. In addition, there is often a failure to properly adjust force when pulling with the arm against an opposing force. As this opposing force suddenly gives way, the patient fails to apply a brake to the action of the arm and tends to have a rebound overshoot. The arm may even strike the body or face.

Finally, patients with cerebellar hemisphere disease are said to have a dyssynergia or disturbance in the synergy of movements, that is a defect of the coordination of multiple sets of agonists and antagonistic muscles when reaching for an object. The result is a decomposition of movement.

Cerebellar Dysarthria may also be present and is characterized by scanning (hesitation) that affects the pattern and intonation of speech. Prosody (rhythm and harmony) is affected rather than word sequence. At times, a tremor of speech is also apparent. Dysarthria may occur in cerebellar atrophy or in focal processes involving the hemisphere or the superior vermis. The crucial area of involvement is the superior paravermal area, as discussed by Amarenco et al, 1991 and Lechtenberg and Gilman, 1978. The left hemisphere is more often involved than the right.

The patient with disease of the cerebellar hemisphere also has a disturbance of gait. This tends to be an ipsilateral disturbance of gait, with a tendency to fall toward the side of the lesion. As discussed above, in lesions of the hemisphere, balance is often well maintained, in contrast to lesions of the floccular nodular lobe, where a disturbance of gait and of sitting balance also occurs. The following case history 20-5 presented on CD ROM illustrates a hemangioblastoma of the right lateral hemisphere with headache, lateralized ataxia, intention tremor and dysmetria of the right upper and lower extremities. At the present time, the diagnosis of these tumors may be readily made by means of MRI and CT scan *(Fig. 20-11)*. Arteriograms may still be of value in defining the vascularity and blood supply of the tumor.

Case 20-6 presented later in this chapter demonstrates a cerebellar infarct with many lateralized appendicular features. A cerebellar hemisphere hemorrhage illustrated later in the chapter also demonstrates many of these lateralized features.

LESIONS OF THE CEREBELLAR PEDUNCLES: (METTLER & ORIOLI, 1958; CARRERA & METTLER, 1947.)

Some patients demonstrating cerebellar symptoms and findings actually have damage to the cerebellar peduncle rather than direct involvement of the cerebellum.

Lesions of the inferior cerebellar peduncle result in an ataxia of the extremities on the side of the lesion, with falling toward the side of the lesion and nystagmus.

Lesions of the superior cerebellar peduncle, the brachium conjunctivum, produce a unilateral ataxia of the limbs, with intention tremor and hypotonia. The symptoms are essentially those of hemisphere lesions. The clinical symptomatology is ipsilateral if the lesion occurs between the dentate nucleus and the decussation of the brachium conjunctivum. If the lesion is above this decussation, the tremor is usually contralateral and often is more than a pure intention tremor. These are components of a sustained postural type of tremor. At times, with involvement of this area within the midbrain, a resting tremor results as well, as discussed in relation to the basal ganglia. It is not unusual to have the tremor evolve from an initial relatively pure intention tremor to a later resting tremor. At times, a minor degree of hemichorea is also present. This is not remarkable when one considers that these areas of the midbrain, the subthalamus and the ventrolateral nucleus of thalamus are close together and all supplied by penetrating branches of the poste-

[5] *Diener and Dichgans (1992) suggest that the terms kinetic, goal-directed or terminal better describe the actual tremor. Defect in movement termination is thus referred to as* dysmetria.

rior cerebral artery. Intention myoclonus may also occur at the onset of movement and may merge with hemichorea.

The effects of isolated lesions of the middle cerebellar peduncles are not certain. There is some evidence that an incoordination of fine limb movements and an ataxia of gait may result. In experimental lesions, circling may result.

VASCULAR SYNDROMES OF THE CEREBELLUM

The development of CT and MRI scan has resulted in an increased recognition of infarcts, hemorrhages, and arteriovenous malformations involving the cerebellum. Many have been clinically silent or previously attributed to brain stem or labyrinthine pathology. We have already considered the blood supply of the cerebellum in Chapter 13, which covers vascular syndromes of the brain stem. Essentially, three circumferential arteries of the vertebral basilar circulation supply the several surfaces of the cerebellum, the arteries being named for the surface they supply:

1. The posterior inferior cerebellar artery (PICA), usually originating from the vertebral artery: an initial medial branch of this vessel supplies the lateral tegmental area of the medulla, and the medial and lateral branches supply the cerebellum.

2. The anterior inferior cerebellar artery (AICA), originating from the lower third basilar artery: the initial branches of this vessel supply the lateral tegmental area of the lower pons.

3. The superior cerebellar artery, originating from the rostral basilar artery: proximal branches supply the lateral tegmental area of the rostral pons and caudal mesencephalon.

All three vessels have extensive leptomeningeal anastomoses over the surface of the cerebellum that are similar to the leptomeningeal anastomoses of the arteries supplying the cortical surface of the cerebral hemispheres. As a consequence, vertebral artery occlusion may result in a lateral medullary infarct and syndrome but infarction of cerebellum may be absent or limited. As in the cerebral hemispheres border zone infarctions may occur. On the other hand, embolic occlusion is frequently implicated in cerebellar vascular syndromes.

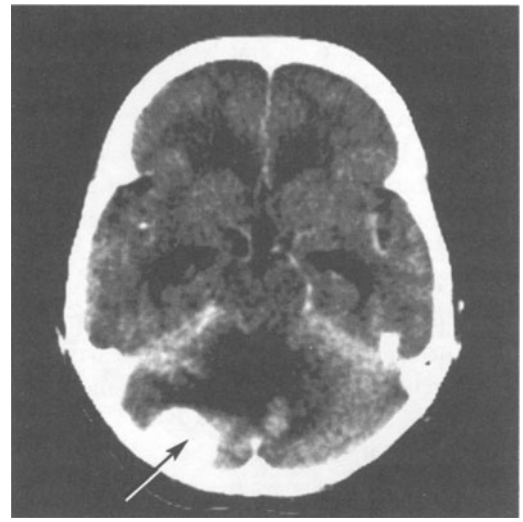


Figure 20-11. Hemangioblastoma of superficial superior and posterior right cerebellar hemisphere. CT scan indicated a densely enhancing mass (arrow) with considerable surrounding edema and cyst formation extending into the opposite cerebellar hemisphere and hydrocephalus. This 60-year-old white female had a several month history of increasing headaches, exacerbated by straining at stool, laughing or any head movement, a sense of dizziness, a sense of instability in walking and a normal neurologic examination. Angiogram demonstrated a vascular mass supplied by the posterior inferior cerebellar and superior cerebellar arteries, as well as meningeal branches. Dr Bernard Stone removed the tumor with relief of symptoms.

SYNDROMES OF OCCLUSION AND INFARCTION:

This topic has been well reviewed by Amarenco (1991), in an article that summarizes the detailed studies of his group (Amarenco et al, 1989; Amarenco et al, 1991; Amarenco&Hauw, 1990a and 1990b). The discussion presented here is in large part based on their studies. Refer also to the detailed reviews of Chaves et.al., 1994 and Kase et al, 1993.

Although autopsy series localized only between 1.5 and 4.2% of all infarcts to the cerebellum, in a CT scan series (Shenkin and Zavala, 1982) cerebellar infarcts accounted for

15% of all intracranial infarcts. Cerebellar infarcts account for 85% of all cerebellar strokes and hemorrhages for 15%; therefore, our emphasis will be on infarcts.

The symptoms of infarcts and hemorrhages may be similar, particularly if the infarct is large and associated with considerable edema. The large infarct may have what is referred to as a "pseudotumor" presentation. Essentially, the patient has the acute onset of headaches (usually localized to the occipital or cervical occipital area), severe vertigo, nausea, vomiting and ataxia of gait (often so severe that the patient is unwilling or unable to sit or stand). On examination, nystagmus and ipsilateral dysmetria on finger-to-nose and heel-to-shin tests will be present. Cerebellar type dysarthria is frequent (particularly when the superior cerebellar artery is involved). Coma at the onset or shortly after onset usually indicates severe edema with probable compromise of the fourth ventricle and/or aqueduct of Sylvius or brain stem. Evolving extraocular palsies are also usually indicative of compromise of the brain stem. MRI scan or CT scan allows the following:

a. distinction between infarct and hemorrhage

b. determination of whether hydrocephalus is present

c. determination of the vascular territory of the cerebellum and brain stem involved.

Patients presenting in coma or evolving into coma due to hydrocephalus and/or brain stem compression require immediate shunting to reduce the hydrocephalus and sometimes require evacuation of the hemorrhage or infarct (Shenkin and Zavala, 1982; Heros, 1982).

This acute presentation has long been recognized, although occasional patients are still initially misdiagnosed as suffering from acute labyrinthine vertigo, as in the example presented below. The majority (80 to 90%) of cerebellar infarcts have a more benign course not requiring surgical therapy. Many are recognized only in retrospect when a CT scan or MRI is obtained to analyze another CNS event. The superior cerebellar artery territory or the posterior inferior cerebellar artery territory are most frequently involved. In our own experience, the symptomatic cerebellar infarct is often in the territory of the posterior inferior cerebellar artery (see case history below and Caplan, 1986,and Chaves et. al., 1996). The anterior inferior cerebellar artery is rarely involved in isolation; the posterior inferior cerebellar territory is often also infarcted. One third of patients with superior cerebellar artery infarcts, also have infarcts within the territory of the posterior inferior cerebellar artery suggesting a possible embolus from the vertebral artery to the more distal basilar artery branches. Although some patients with infarcts in the distribution of the posterior inferior cerebellar artery will also infarct the associated brain stem territory and present a lateral medullary infarct syndrome as in case 13-2, the majority have isolated cerebellar infarcts. In contrast most patients with cerebellar infarcts of the anterior cerebellar artery territory also have infarcts of the caudal lateral tegmental pontine territory. Most patients with cerebellar infarcts of the territory of the superior cerebellar artery have associated infarcts in the brainstem territory of the rostral basilar artery. It is therefore easy to see that prior to the era of CT/MRI, the clinical features of the associated brain stem infarction (that included involvement of the cerebellar peduncles) dominated the picture and obscured the infarct of the cerebellum. More limited infarcts of parts of the superior cerebellar (lateral and medial) and posterior inferior cerebellar artery (dorsomedial and lateral) or of the cerebellar border zones are discussed in the various papers of Amarenco. The etiology for most infarcts involving the superior cerebellar artery is embolism of cardiac source. Posterior inferior cerebellar artery infarcts are either embolic of cardiac source or due to atherosclerotic occlusion of the vertebral (or less often) the posterior inferior cerebellar artery.

The following case history presents a typical example of posterior inferior cerebellar artery infarct, the territory most frequently affected selectively.

Case 20-6: This 64-year-old right-handed married white male postmaster, on the morning prior to admission, awoke at 3:00 a.m. with severe posterior headache and severe vertigo, which was exacerbated by any head movement ,nausea, projectile vomiting and slurred speech. Shortly afterwards, he noted left facial paresthesias, clumsiness of the left upper extremity, and diplopia. Two weeks previously, the patient had been seen for a transient episode of difficulty controlling the right arm, a hissing sensation, and impairment of speech *Past history* was significant for hypertension, coronary artery bypass surgery, and six years previously episodes of. transient weakness and numbness of the right arm with transient aphasia for which he had been placed on long term anticoagulation. At that time he had normal aortic arch and carotid angiographic studies but EEG had demonstrated focal left frontal/temporal slow wave activity

Neurologic examination: *Cranial Nerves:* Conjugate lateral gaze to the left was impaired. *Motor System:* Lateralized cerebellar findings were present with marked dysmetria of left upper extremity on finger-to-nose testing and impairment of alternating hand movements. In attempting to stand, the patient was markedly ataxic. *Reflexes:* Deep tendon stretch reflexes were decreased in both lower extremities. Plantar response was extensor on the right and flexor on the left.

Clinical diagnosis: The acute onset of headache, vertigo, vomiting, ataxia of gait, and dysmetria of the left arm were consistent with a left cerebellar hemisphere infarct or hemorrhage with possible minor involvement of brainstem secondary to mass effect.

Laboratory data: *CT scan* demonstrated a large left cerebellar infarct pressing the fourth ventricle to the right. *Magnetic resonance angiography* demonstrated occlusion of the left vertebral artery. *MRI* (2months after onset of symptoms): Infarction of the total cerebellar territory of the left posterior inferior cerebellar artery with no actual infarct of the brain stem *(Fig.20-12).*

Subsequent course: The patient was somewhat vague with some difficulty in memory during the subsequent 8-day hospital course and remained ataxic. He had three weeks of intensive rehabilitation with continuous subsequent improvement. Evaluation 6 months after onset of symptoms demonstrated only a slight slowness of alternating movements of the left hand.

A final note should be made regarding the considerable ability of the human nervous system to recover from extensive cerebellar lesions. Considerable recovery is possible because the cerebellum does not have a direct line role in the control of motor activity but instead, acts as a modulator of the motor control and motor planning circuits.

Causes of Hemorrhage into the Cerebellum.

1. *Hypertensive Hemorrhage Into the Cerebellum.* The cerebellum is the site of hypertensive hemorrhage in 8 to 10% of all cases. In the era before CT scan and MRI, only large hemorrhages or fatal hemorrhages were recognized *(see Figure 20-13a).* Smaller lesions were not well localized. These are now clearly seen *(Fig.20-13b).* Either the hemisphere (the hemorrhage often originates in the region of dentate nucleus) or vermis may be involved (Kase and Caplan, 1986).

2. *Arteriovenous Malformations.* The cerebellum is also the site of various types

Before the era of CT and MRI, the precise diagnosis was often not established. Small hemorrhages might have only nonspecific symptoms of headache and dizziness, as in case 20-7, and *Fig. 20-14* presented on CD-ROM.

SPINOCEREBELLAR DEGENERATIONS

In addition to those nutritional and systemic processes that involve primarily the cerebellar cortex, other diseases, usually genetic, involve the cerebellum as part of a degeneration .Other systems may be involved in addition to the cerebellum We can only briefly outline this very extensive topic which has been an area of rapid research advances.

In classifying these disorders ,we will follow

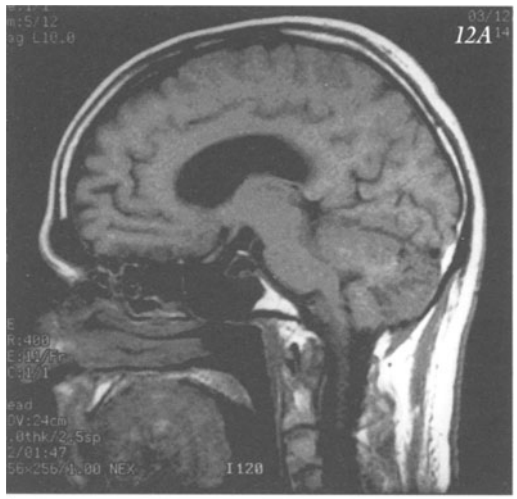
the approach of Wood and Harding (2000), adding more recent genetic information of Klockgether et al (2000) and Fujigasaki et al (2001) .

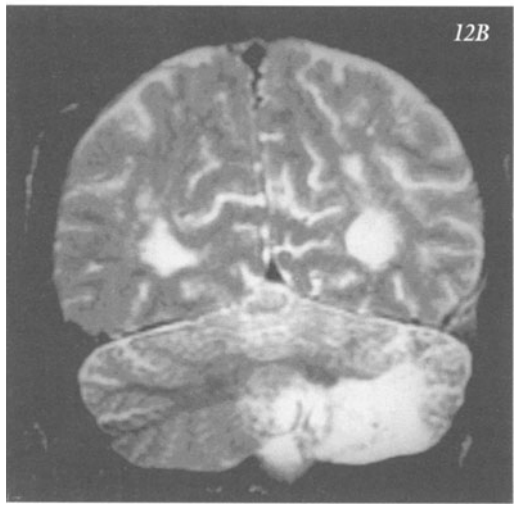
The first step in classification is to separate all of these ataxic disorders into two main categories.

I.The autosomal recessive cerebellar ataxias are usually of early onset, (< 20 years of age).

II.The autosomal dominant cerebellar ataxias (ADCA) are usually of late onset, (>20 years).

I. Autosomal recessive disorders: The most common disorder in this category is Freidreich's ataxia which accounts for at least 50% of all cases of hereditary ataxia reported in large series from the United States and Europe.





This disorder which has a prevalence of 1-2 per 100,000, maps to chromosome 9q13. The mutation involves the trinucleotide repeat GAA. The normal number of repeats is 7-22, but in patients with Friedreich's ataxia there are 100-2000 repeats. The marked multiplication undoubtedly explains the early onset and severity of the disease. The gene product is a protein, frataxin. Refer to Chapter 9 for additional discussion.

Other rare disorders in this category include the following.

a) cerebellar ataxia with retained deep tendon reflexes reflexes,in which a mutation in the frataxin gene also occurs. The cases are less severe than Freidreich's ataxia, but with greater cerebellar atrophy on imaging studies.

b) cerebellar ataxia with hypogonadism in which there is predominant involvement of cerebellum and inferior olivary nuclei.

c) cerebellar ataxia with myoclonus(formerly called the Ramsay Hunt syndrome or dyssynergia cerebellaris myoclonica) but now recognized to be a heterogeneous syndrome. Included in this category are such entities as 1) the mitochondrial disorder ,myoclonus epilep-

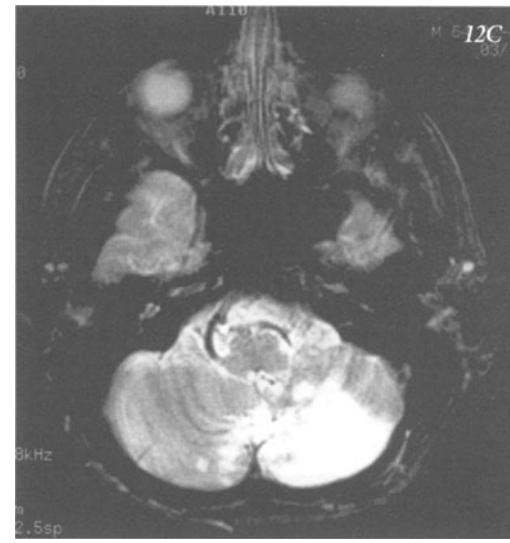


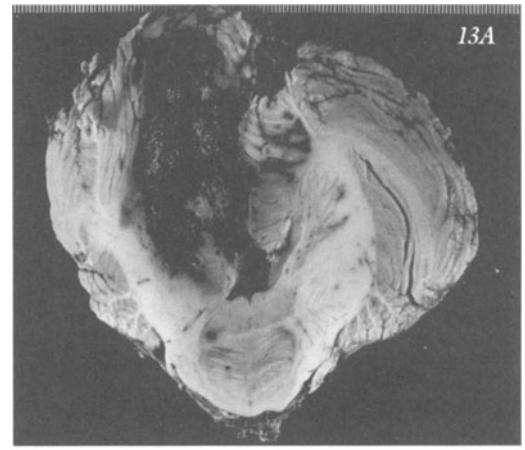
Figure 20-12: Cerebellar infarct in posterior inferior cerebellar artery territory. Case 20-6. Refer to text. MRI: A) T1 weighted sagittal section 10 mm to left of midline. B) T2 weighted posterior coronal section. C) T2 weighted axial sections at level of upper medulla inferior olive.

sy with ragged red fibers (MERRF) and 2)myoclonic epilepsy of Unverricht& Lundborg (Baltic myoclonus or EPM1) .The gene locus which maps to chromosome 21 encodes a small protein cystatin B whose role in the neurological disease is unclear.

d) other rare disorders in which cerebellar ataxia is associated in various combinations with deafness, or optic atrophy or mental retardation or cataracts or retinopathy.

e) There are also a whole host of relatively rare inherited usually autosomal recessive metabolic disorders in which progressive cerebellar ataxia may be a prominent feature. One group of disorders involves deficiencies in vitamin E due to genetic mutations or to malabsorption syndromes such as cystic fibrosis. Some of these disorders might be treatable with administration of vitamin E.

An additional disorder carries the designation ataxia telangiectasia. This is an autosomal recessive disorder, with onset of a progressive cerebellar ataxia beginning in the first 1 to 2 years of life followed by the development of choreoathetosis. One in 40,000-1000,000 live births is affected. An associated finding in all cases, usually appearing by age 6, is the presence of telangiectasis or capillary dilatation of severe and progressive degree, initially involving the conjunctiva but then appearing over the face and neck and the flexor surfaces of the limbs (antecubital and popliteal areas). The neuropathology primarily affects the Purkinje and granule cells of cerebellar cortex. These patients have severe medical problems related to the immune system, affecting both cellular and humoral immunity. The thymus remains in a fetal state. The patients have a marked sensitivity to ionizing radiation and to radiomimetic chemicals, as studied in cultured fibroblasts. The mutation which has been linked in some cases to chromosome 11q results in a defect in repair of DNA. The defective immune state results in a susceptibility to infectious diseases. There is a marked increase in malignancies, particularly leukemia and lymphomas, with rates which are 61 to 184 times normal. More recently, studies of the heterozygotes (who



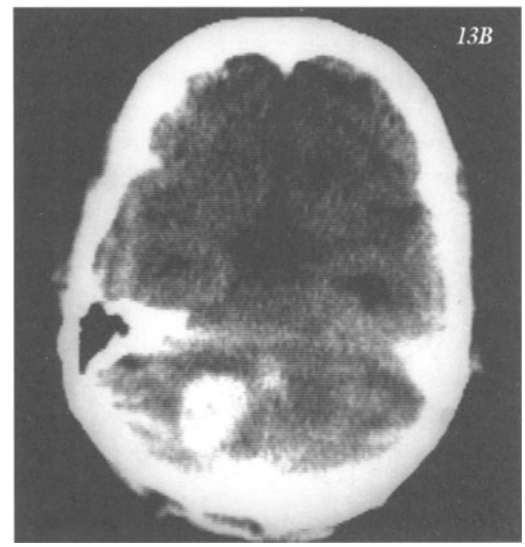


Figure 20-13: A) Large midline-paramedian cerebellar hemorrhage with rupture into the ventricle. This hypertensive (240/110) 61-year-old male had sudden onset of headache, vomiting dizziness, ataxia of gait and trunk, nystagmus on left lateral gaze and minor incoordination of the left hand. (Courtesy of Dr.John Hills and Dr. Jose Segarra.) B) Large hypertensive hemorrhage into right cerebellar hemisphere with hydrocephalus. CT scan (non-enhanced). This 65-year-old white male who had hypertension, diabetes, congestive heart failure and alcoholism, developed over one hour, vomiting, and a marked ataxia of gait. Examination indicated severe ataxia of gait, marked horizontal nystagmus on gaze to the right, dysmetria on right finger-to-nose and heel-to-shin tests, plus a mild right Horner's syndrome and a mild dysarthria, and bilateral Babinski signs. Symptoms resolved over several weeks.

constitute 1% of the general population but do not have neurologic symptoms) have demon-

strated a significant increase in cancer rates, with an overall rate approximately 3.5 times that in the general population and breast cancer rates in females 5 times those in the control population. Diagnostic or occupational exposure to ionizing radiation increases the cancer risk of the heterozygotes compared to the controls (Swift et al, 1991).

II. Autosomal dominant disorders: These disorders were a problem in classification.The names of the authors of the various papers describing the clinical features and neuropathology of each of the groups of cases or families were attached as labels and included many of the famous neurologists of the late 1800s and early 1900s such as Holmes, Andre Thomas, Marie, Foix and Alajounine (Greenfield, 1954).Holmes separated these disorders into spinocerebellar degeneration, relatively pure degeneration of the cerebellar cortex and olivopontocerebellar degeneration. More recently Harding (1982), proposed a clinical classification into three major categories of which the first type is the most common

ADCA I: cerebellar ataxia is accompanied at some point in evolution by supranuclear ophthalmoplegia, optic atrophy, basal ganglia symptoms, dementia and amyotrophy.

ADCA II: in addition to the above has retinal degeneration.

ADCA III: presents a relatively pure cerebellar syndrome .

ADCA IV: is a recent addition to the classification cerebellar ataxia is combined with epilepsy.

The problem with all of these classifications from a clinical diagnostic standpoint was that early in the disease, all three groups might have predominantly cerebellar features. With the unraveling of the molecular genetic basis of the diseases, the **term ADCA has been replaced by the term spinocerebellar ataxia (SCA).** To date, 12 different loci have been identified and in many of these the molecular mechanism has been identified (SCA 1-SCA12)*. The gene products of the SCA genes are termed ataxins and are assigned a similar number .In addition 2 channelopathies causing episodic ataxias have been identified as EA 1 and 2.

Gene mechanisms:

1) CAG trinucleotide expansion: SCA 1,2,3,6 ,7, and 12 all involve an expansion of the CAG trinucleotide repeat as in Huntington disease (chromosome 4p16.3) but the chromosome loci are different (SCA 1 @ 6p, SCA 2 @ 12q, SCA 3 @ 14q, SCA 6@19p, SCA 7 @ 3P, SCA 12 @5). This expansion is translated into proteins with expanded polyglutamine tracts. At the ultra structural level, these expanded proteins are found in neuronal intranuclear inclusions.

2) CTG trinucleotide expansion: SCA 8 is a CTG expansion on 13q, the same type of trinucleotide expansion found in myotonic dystrophy.

3) Channelopathy: In EA 1 there is a point mutation in a potassium channel on chromosome 12. In EA 2 there is a point mutation in a calcium channel on chromosome 19q.

Patients with EA 1 have frequent brief attacks lasting minutes of ataxia plus myokymia (a muscle rippling due to peripheral motor nerve hyperexcitability). The patients are normal between attacks. Some cases benefit from acetazolamide or phenytoin. Patients with EA 2, have longer attacks lasting hours to days involving severe truncal ataxia plus vertigo and vomiting. The patients respond well to acetazolamide. However nystagmus is noted between attacks and over the years a slowly progressive ataxia develops. The MRI study at that point will confirm the cerebellar atrophy.

SCA 6 also has features of a channelopathy in that the CAG expansion occurs in a gene that encodes a voltage dependent calcium channel. The chromosome location19 is similar to EA 2.

4). Unknown: The mechanisms involved in SCA 4, SCA 5, SCA 10** and SCA 11 are

** As of April, 2002, the number of identified loci has grown to 17. SCA 17 involves a CAG trinucleotide expansion. There is an overlap with basal ganglia disorders for a binding protein.*

*** SCA 10 has now been associated with a pentaneuclotide expansion.*

at the present time unknown. The chromosome locations are SCA 4@16q, SCA 5 @11 centromere, SCA 10 @22q and SCA 11 @ 15q.

Relationship to the clinical classification: SCA 1, 2, 3, and 12 correspond in general to ADCA I. Whether, SCA 2 or SCA 3 is the most frequent mutation depends on the series reviewed (Giunti et al, 1998 and Klockether et al 1998)*

SCA 7 corresponds to ADCA II.

SCA 5, 6 ,8 and 11 correspond to ADCA III. SCA 5 however has some posterior column features .SCA 6 has some sensory and pyramidal features and thus could be placed in the ADCA I group.

SCA 4 has cerebellar features plus a sensory neuropathy and probably would have been classified as ADCA I.

SCA 10** combines cerebellar ataxia with epilepsy (ADCA IV).

Azorean Disease: Machado-Joseph Disease: Refer to the reviews of Rosenberg (1992) and Sudarsky et al (1992).

This autosomal dominant spinocerebellar degeneration is clustered among families who originated in the Portuguese Azorean Islands. This is the region of origin for many families residing in Southeastern Massachusetts and the adjacent area of Rhode Island, and the initial cases were described in this area in 1972. Subsequently, other cases have been described in many areas of the world reached by Portuguese seafarers, explorers, whalers, and fishermen (many of whom were recruited in the Azores). The manifestations depend in part on the age of onset.

I. Early onset (childhood or young adult) cases have predominantly pyramidal and features and basal ganglia dysfunction.

II. Intermediate age of onset (20 to 40 years) Cases have cerebellar deficits and extraocular disturbances as well as the pyramidal features and basal ganglia dysfunction.

III. Later onset (50 to 60 years). Cases are characterized by cerebellar deficits and peripheral neuropathy.

IV. Possible late onset case may have a peripheral neuropathy plus Parkinsonism.

Since the molecular basis of the disorder is now clear, the more specific molecular diagnosis should be utilized when possible: most families carry the SCA 3 mutation. Occasionally the SCA 1 or the SCA 2 mutations have been found. In contrast to OPCA to be discussed below, the cerebellar cortex and the inferior olivary nucleus are not involved. The ataxia instead correlates with a degeneration of the afferent and efferent cerebellar systems (spinocerebellar tracts and Clarke's column dorsal nucleus) and the lid retraction and other extraocular features reflect involvement of the periaqueductal and third nerve nuclear areas.

Olivopontocerebellar Atrophy (OPCA):

This diagnosis once included many of the cases subsequently described as ADCA or SCA. When cases of progressive adult onset ataxia are familial, they should be assigned a diagnosis based on the genetic classification described above. This entity also has been considered in chapter 19 on the basal ganglia and is one of the multisystem atrophies considered in the general category of Parkinsonism plus syndromes. In contrast to the data presented in that chapter, Berciano(1988),when considering both familial and sporadic cases of OPCA.; found cerebellar symptoms (predominantly gait ataxia) to be the most common initial symptom (73%) and the most frequent symptom throughout the course of the disease (88-97%). Parkinsonian symptoms occurred as the initial feature in 8% but eventually in 35-57%. The neuropathology involved in all cases the cerebellar cortex, the pontine nuclei and the inferior olivary nuclei with associated changes in the white matter of cerebellar peduncles (particularly the middle) and of the cerebellar white matter. The substantia nigra is involved in 50% of cases.

Non familial cases of ADCA: Wood and Harding (2000)estimate that approximately two thirds of cases of degenerative ataxia

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**A recent addition to this CAG expansion group is DRPLA- (rubro pallido luysian atrophy) a basal ganglia disorder.*

*** and SCA 17*

beginning after age 20 are single cases without a family history, and suggest that the term idiopathic late onset cerebellar ataxia be utilized rather than the old term OPCA. The majority of cases do demonstrate the pathological findings of OPCA. Some will go on to develop the autonomic features of multisystem atrophy. Some of the patients with onset after age 55 years will demonstrate a relatively pure midline cerebellar syndrome with primarily gait ataxia related to cerebellar atrophy which is most marked in the vermis. With tests for the molecular basis of the disease now available (particularly as regards the trinucletide expansions),the number of such sporadic unclassified cases should be reduced. Note that families have become smaller, full family historical information is not always available. There are however other entities to be considered when faced with a sporadic case.

Alcoholic nutritional cerebellar degeneration: refer to discussion above in relation to anterior lobe.

Paraneoplastic subacute cerebellar degeneration: This degeneration is associated particularly with cancer of the ovary , breast, small-cell cancer of the lung and Hodgkin's disease. The neurologic symptoms may precede the discovery of the primary malignancy in the majority of these patients except in those with Hodgkin's disease where the diagnosis of the malignancy usually has already been established. In general, these patients present with subacute onset of cerebellar symptoms affecting stance, gait, limbs and voice (dysarthria). The neuropathology involves a widespread loss of Purkinje cells and evidence of inflammation. The brain stem and dorsal root ganglia and possibly the limbic system may also show inflammatory changes, as part of a wider "encephalitis". Anti-Purkinje cell antibodies can be identified in many of these patients. Anti-yo antibodies which involve the Purkinje cell cytoplasm are found in patients with ovarian cancer, breast cancer or other gynecological malignancies. Patients with Hodgkin's disease who develop the cerebellar syndrome may have antibodies to a glutamate receptor (Smitt,et al 2000) The paraneoplastic syndromes may improve with control of the primary malignancy. Note, however, that the late cases have evidence on CT or MRI of cerebellar atrophy.

AN OVERVIEW OF TREMORS

Before concluding our discussion of the cerebellum and basal ganglia, we will briefly outline the various types of tremor. This is necessary because many common postural tremors (physiologic and essential) are mistakenly attributed to more serious disease of the basal ganglia or cerebellum.

Tremor is defined as an involuntary movement characterized by rhythmic oscillation of a body part (or parts) that develops when there is a synchronized discharge of many motor units. Many peripheral and central factors enter into this synchronization. Hallett, 1998, Elble, 1998, and Hua discuss the physiology of tremor and the role of mechanical factors and central oscillators, 1998.

Tremor is best classified on the basis of the behavioral situation in which the tremor is observed (Findley, 1988; Hallet, 1991, Deuschl, 1998): **1. tremor at rest 2. action tremor. Within this second category, postural, kinetic, or intention, and task-specific tremors are distinguished.**

1. **Rest Tremor:** This is a tremor that occurs in a body part that is not voluntarily activated and is completely supported against gravity. This tremor particularly when a pill-rolling component is present, is almost always indicative of Parkinson's disease or of related disease of the basal ganglia.

2. **Action tremors:** This is a tremor that is produced by voluntary contraction of muscle. Within this category several subtypes may be specified:

a. **Postural tremors:** These are by far the most common types of tremor and include:

1. *Physiologic Tremor* - usually fine and rapid (6 to 12 Hz), occurs when attempting to sustain a posture. This tremor is significantly increased or "enhanced" by anxiety, excessive caffeine intake, exercise, fatigue. It is also

increased by thyrotoxicosis, hypoglycemia, alcohol withdrawal and beta adrenergic drugs, such as those used in the treatment of asthma and by drugs commonly employed in psychiatry, such as lithium, neuroleptic, or tricyclic medications. Beta adrenergic blockers such as propranolol are often effective against this tremor if specific etiologic factors cannot be corrected (use in asthmatics, however, is contraindicated).

2. *Essential Tremor:* also called familial, benign, or senile tremor: Aside from physiologic tremor, essential tremor is the most common tremor encountered by the physician. Prevalence studies suggest a high frequency, particularly in older age groups. In the over 40 age group, 5% of the population may be affected. When familial, the genetic pattern appears to be autosomal dominant. Onset of familial cases may begin in childhood, adolescence, in mid life, or later in life. The hands are most commonly affected, but in some patients, the head is primarily involved (side-to-side movement). Some also have involvement of the voice or lips. The frequency of tremor ranges from 4 to 12 Hz. The tremor may remain stable or may slowly progress. Although in some patients the tremor is of relatively small amplitude, in other patients it may become relatively coarse, significantly interfering with fine motor activities. Orthostatic tremor is a variant in which a tremor of trunk and legs and to a lesser degree of arms occurs on prolonged standing and is associated with a high frequency of contractions alternating between antagonist muscles.

The underlying pathology of essential tremor is unknown. Functional imaging studies at rest and on action suggest an abnormal bilateral overactivity of cerebellar connections Infarcts (homolateral) of the cerebellum or of contralateral motor cortex or of ventrolateral thalamus may result in the disappearance of the tremor (Dupuis et al,1989). Typical of essential tremor is the temporary reduction in the tremor by ingestion of alcohol. The tremor usually responds to beta adrenergic blockers, such as propranolol. Note that in essential tremor, Parkinsonian and cerebellar features are absent: thus, the patient is able to walk with a good swing of the arms and does not turn en bloc. No pill rolling tremor emerges as the patient sits at rest or walks. No ataxia of gait or stance is present. These distinctions are of importance because postural tremors (of the outstretched hands) can also occur in patients with clear-cut evidence of akinetic rigid variants of Parkinson's disease, Wilson's disease, dystonia and cerebellar disease. A postural tremor may also occur in some forms of peripheral neuropathy or in post traumatic syndromes.

b. **Kinetic tremors** (usually approximately 5 Hz).These are tremors occurring during any voluntary movement. Several types have been specified:

1. *Tremor during target directed movements: intention tremor.* Amplitude increases during visually guide movements towards a target particularly at the termination of movement. This tremor usually is characteristic of cerebellar disease and is described in detail above. Intention tremor is an oscillation perpendicular to the line of movement. Findley (1988), distinguishes the tremor from dysmetria, defining the latter as "the inability to attain the target or normal performance level in a guided, goal-seeking movement. The more severe and violent kinetic tremors are seen in patients with severe multiple sclerosis involving both the brain stem and cerebellum. In these cases, the head and trunk may have a to-and-fro, anterior-to-posterior sway, or tremor, to which the term "titubation" has been applied (Findley, 1988). Cerebellar intention tremor may be decreased by lesions of the contralateral ventral lateral thalamic nucleus as discussed in chapter 19 .

2. *Task specific kinetic tremor: Kinetic tremor which appears or becomes exacerbated during specific activities related to occupation or writing.* It is uncertain whether primary writing tremor and some of the occupational tremors of musicians etc, represent a variant of essential tremor or of dystonia as discussed by Hallet (1991)