1 The cerebellum

Introduction

It may come as a surprise to know that the cerebellum (literally "little brain") has nearly as many neurons as the entire cerebrum. While the cerebellum has, at various epochs, been postulated to be the seat of love or of sexual desire in the CNS, we now know that its main function is to assist the primary motor system in the control of motion. This includes helping to control equilibrium, posture, eye movements, and the control of voluntary movements through careful monitoring of their strength, velocity, and trajectory. Recent research is also revealing that the cerebellum may have significant non-motor functions, including some input in cognition.

While neuroanatomists often describe the cerebellum as "simple" in structure, "uniform" may be a better word. Detailed descriptions of the different cell types, neuronal connections, feedback loops between different cell populations, which cells are inhibitory and which are excitatory, etc., is at this time of little clinical significance. This is because, although the cytoarchitecture has been well described, the link between this and how the cerebellum actually performs its functions remains unclear. Therefore, we will give only a brief and necessarily incomplete description of microscopic anatomy, followed by a discussion of cerebellar functional zones, which is clinically more relevant.

Anatomic overview

The cerebellum can be thought of as a white matter core covered by convolutions of gray matter cortex called folia. Imbedded within the white matter core are four pairs of deep cerebellar nuclei, all adjacent to the fourth ventricle (Fig. 1.1). Moving lateral to medial, they are the dentate, emboliform, globose, and fastigial nuclei. The emboliform and globose nuclei are a single functional unit and are therefore often referred to as the interposed nucleus.

The motor and premotor cortex of the cerebrum communicate with the cerebellar cortex regarding planned movements, while essentially all sensory modalities also input into the cerebellar cortex to apprise it regarding the status of movements in progress. The cerebellar cortex processes this very complex information and sends its output to the deep cerebellar nuclei, which communicate back to the cerebral cortex.

Therefore, at heart, the organizational schema seems straightforward: motor cortex to cerebellar cortex to deep cerebellar nuclei back to motor cortex (Fig. 1.2).

We have found, though, that medical students and junior residents are sometimes confused about this basic schema. When asked, "How does the cerebellum help modulate the motion of my finger to touch my nose? Is it by communicating with the anterior motor horn cells of my cervical spinal cord to control my arm muscles or by communicating with my cerebral cortex?", well over half of those asked believe that the cerebellum modulates a finger-to-nose movement by communicating with the spinal cord. However, it actually does so mainly by communicating with the cerebral cortex. There are some indirect communications with the spinal cord through the red nucleus, as well as through the vestibular and reticular nuclei of the brainstem through the vestibulospinal and reticulospinal tracts respectively. These pathways are especially important for automatic functions such as posture, and for programmed movements such as walking.

Cytoarchitecture

So what then is this cerebellar cortex which does all of this processing? It is composed of three cellular layers (Fig. 1.3). The most superficial of these is the molecular layer, a region filled primarily with axons and dendrites and only a few cells. Next is a single layer of large distinctive neurons known as the Purkinje cells. The third and deepest layer is the granule cell layer composed mostly of neurons called "granule" cells. Both the molecular layer and the granular layer contain some specific types of intrinsic cerebellar neurons such as Golgi cells, stellate cells, and basket cells, but we won't be concerned with that level of detail.

With a modicum of inaccuracy, we can consider the Purkinje cells as the key players in the cerebellar cortex. All

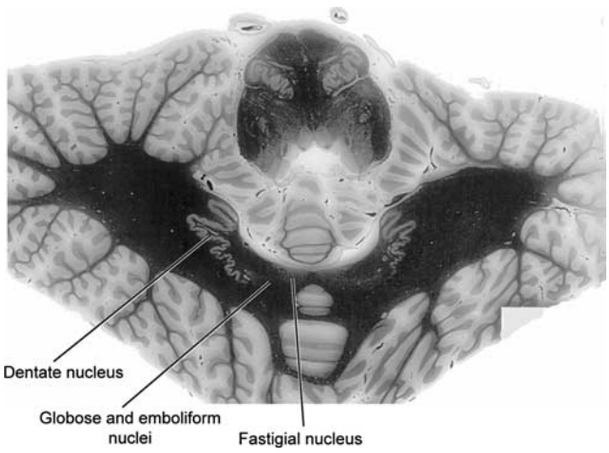


Fig. 1.1. **Anatomic diagram showing the deep cerebellar nuclei.**

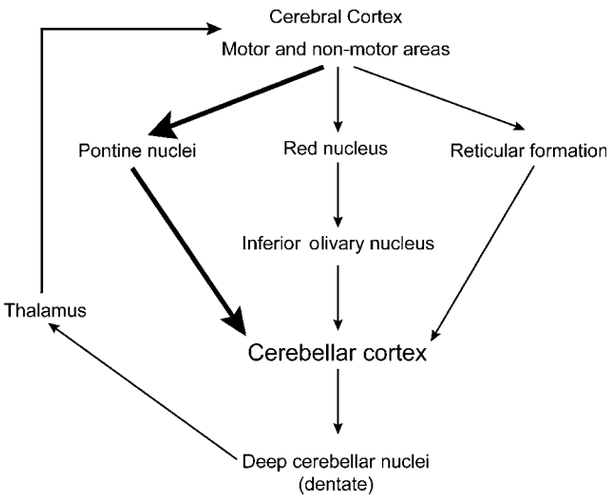


Fig. 1.2. **Schematic diagram showing the basic organizational schema of cerebellar communication. The cerebral cortex communicates with the cerebellar cortex through a main pathway which relays in the pons and through accessory pathways that involve the red nucleus and the reticular formation. These pathways constitute afferent or input information to the cerebellar cortex. After processing these inputs, output (efferent) information from the cerebellar cortex is relayed to the deep cerebellar nuclei, which then communicate back to the cerebral cortex via thalamic relays.**

inputs eventually come to them, and they are the only cells that are able to project outside the cerebellar cortex. They send their axons to the deep cerebellar nuclei, which then communicate the output of the cerebellum to the remainder of the brain.

There are only two ways for incoming (afferent) information to reach the Purkinje cells: either through *climbing* fibers or *mossy* fibers. The climbing fibers to one cerebellar hemisphere arise predominantly from the contralateral inferior olivary nucleus of the medulla. Each climbing fiber ends on one Purkinje cell. The mossy fibers, on the other hand, deliver their information to the Purkinje cells indirectly. They synapse on granule cells in the granular layer, which in turn send their axons to the molecular layer where they synapse with the dendrites of the Purkinje cells.

The mossy fibers arise from three principal afferent sources:
(1) the cerebral cortex, which sends large numbers of cortico-cerebellar fibers that relay on pontine nuclei and then enter the cerebellum;
(2) the vestibular nuclei;
(3) the spinal cord.

The inferior olivary nuclei, the source of climbing fibers, receive information from multiple sources, such as the contralateral spinal cord and, most prominently, the ipsilateral red nucleus. The red nucleus receives multiple inputs to pass to the inferior olives and then the cerebellum, such as prominent cortical inputs, as well as a significant input from the dentate nucleus of the cerebellum, forming a feedback loop.

All communication (afferent and efferent) between the cerebellum and the rest of the CNS takes place through three fiber tracts, known as the inferior, middle, and superior cerebellar peduncles.

Inferior cerebellar peduncles

These are also known as the restiform and juxtarestiform bodies, and bring inputs (afferents) to the cerebellum. The major afferent tracts in the restiform body are the dorsal spinocerebellar tract, the cuneocerebellar tract, and the olivocerebellar tract, arising in the contralateral inferior olivary nucleus. The juxtarestaform body contains axons from the vestibular system. Efferent information from the cerebellum originates from the fastigial nuclei, and terminates in the brainstem.

Middle cerebellar peduncles

These are also known as the brachium pontis. They are an input tract to the cerebellum, originating from the pontine nuclei. There are no efferent axons in the middle cerebellar peduncle.

Superior cerebellar peduncles

These are also known as the brachium conjunctivum. They have a minor input from the spinal cord, but are primarily a major output pathway of the cerebellum. They contain the important dentatothalamic tracts, from the dentate nucleus to the thalamus, as well as outputs from the interposed nuclei, which terminate in the brainstem.

Thus, in rough terms, we can think of the inferior and middle cerebellar peduncles as the input pathways to the cerebellum, carrying inputs from the spinal cord and the cortex, respectively, and the superior cerebellar peduncles as the major output pathway of the cerebrellum. There are some exceptions. For example, the ventral or anterior spinocerebellar tract enters the cerebellum through the superior cerebellar peduncles – but we're thinking BIG PICTURE here!

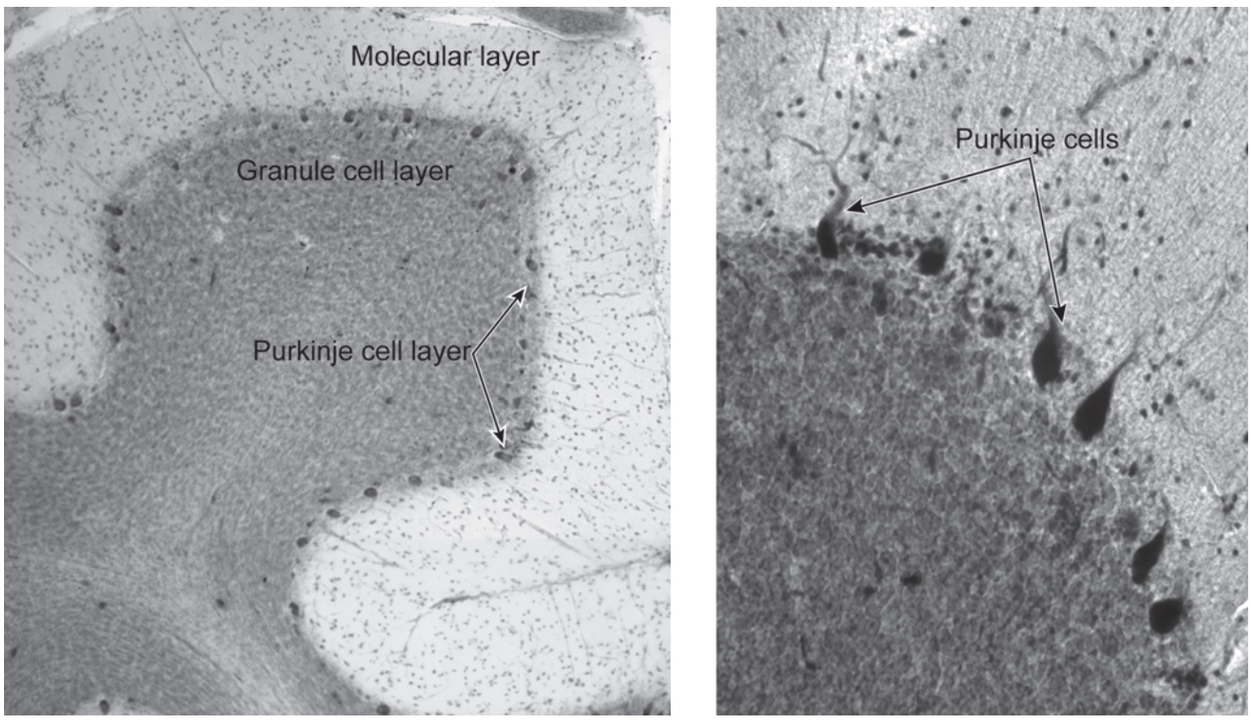


Fig. 1.3. **Cytoarchitecture of the cerebellum. On the left is a photomicrograph of a single folium, showing the loosely packed molecular cell layer adjacent to the pia, and the deep granule cell layer adjacent to the cerebellar white matter. Between these two is a single layer of Purkinje cells. On the right is a magnified view of the Purkinje cells.**

Macroscopic organization

The cerebellum is formed from a midline vermis and two laterally placed cerebellar hemispheres (Fig. 1.4). These can be further subdivided both transversely and longitudinally into clinically meaningful subdivisions. The transverse division of the cerebellum is anatomic, based on the existence of transversely oriented fissures, which divide the cerebellum into three main lobes (each of which contains portions of the vermis and the hemispheres). The primary fissure divides the cerebellum into anterior and posterior lobes. Also, a posterolateral fissure nearly pinches off the flocculus of the cerebellum from the main body, thus forming the flocculonodular lobe, which includes the flocculi as well as the nodulus (a lobule) of the vermis.

Sensory inputs from the head and body are somatotopically mapped three times in the cerebellum – once in the anterior lobe and twice (on each side of the midline) in the poserior lobe, with the trunk toward the midline and the extremities more laterally.

The cerebellum can also be divided longitudinally based on neuronal connections delineating three different functional zones. These are the midline vermis, the intermediate or paravermal zones, and the lateral zones on each side of the vermis. There is some overlap with the previously defined transverse divisions, especially the flocculonodular lobe, which acts as its own functional zone (Fig. 1.5(a), (b)).

Each of these functional zones has fairly distinctive inputs and outputs, leading to important clinical correlations which will be discussed below. Here, we note that each zone sends its output to a different deep nucleus. The lateral zones send their output to the dentate nucleus, the paravermal zones to the interposed nucleus, and the vermis to the fastigial nucleus.

Functional zones and clinical correlations

The lateral zones

These form the bulk of the cerebellar hemispheres. Their major neural connections have been briefly discussed already, and are mostly in the form of a neural circuit between the cerebrum and the cerebellum. Therefore, the lateral zones are also called the *cerebrocerebellum* or the *neocerebellum*. To give a concrete example, let us follow information from the left motor and premotor cortex regarding a planned movement of the right hand, such as a finger-to-nose motion. This information passes through the left internal capsule into the left cerebral peduncle and then into the left pons. In the pons, the axons synapse on pontine reticular neurons and decussate across the belly of the pons (from left to right, in this example). That is why the belly of the pons appears to have horizontal striations on photomicrographs. The axons then enter the right cerebellum via the large right middle cerebellar peduncle. As an aside, this corticocerebellar pathway is significantly

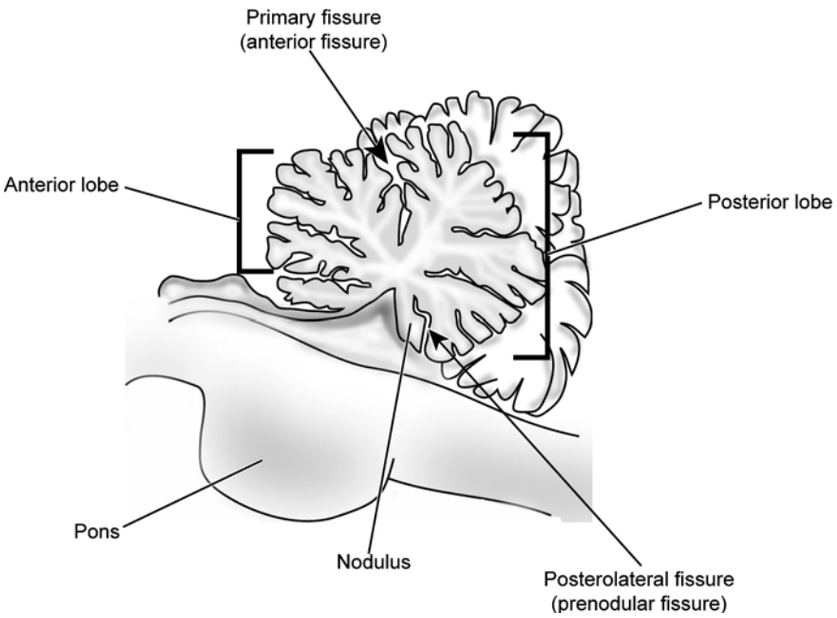


Fig. 1.4. **Schematic diagram of a mid-sagittal slice through the cerebellum and brainstem, outlining the anterior and posterior lobes. The location of the flocculonodular lobe is marked by the nodulus of the vermis, lying just above the posterolateral fissure.**

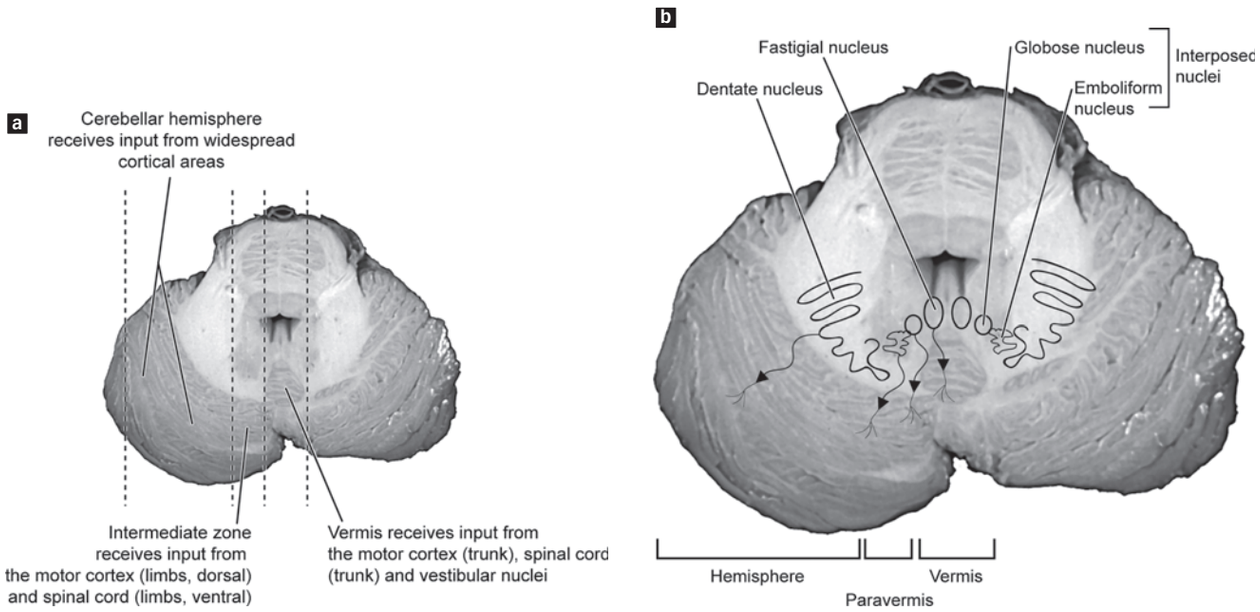


Fig. 1.5 **(a) Schematic showing the different longitudinal functional zones of the cerebellum, and outlining their (a) main inputs and (b) outputs. Note that the lateral zones (hemispheres) output through the dentate nucleus, the paravermal zones output through the interposed (globose and emboliform) nucleus, while the vermis outputs through the fastigial nucleus.**

larger than the corticospinal tracts, perhaps by as much as 20 : 1 in terms of the number of axons.

This afferent information is processed in the cortex of the right cerebellar hemisphere, and the Purkinje cells of the cerebellar cortex send their axons to the right dentate nucleus, which in turn sends its axons out through the right superior cerebellar peduncle. The superior cerebellar peduncles decussate in the caudal midbrain, and the axons pass to the motor nuclei (VA/VL) of the left thalamus (via the dentatothalamic tract). The left thalamus, in turn, projects back to the left

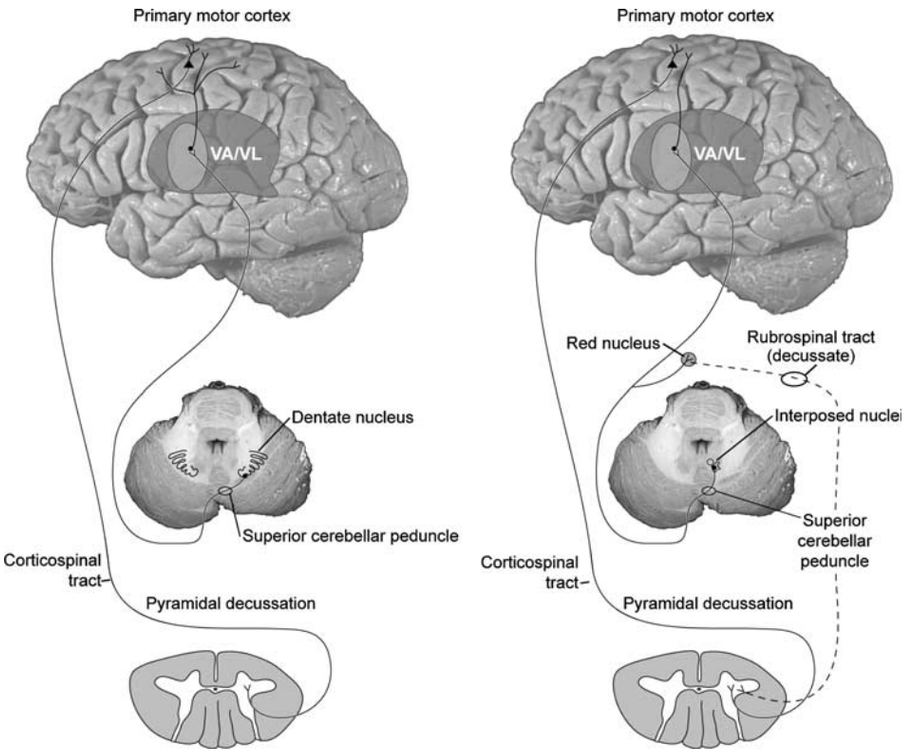


Fig. 1.6. **Schematic diagram of the main output circuits of the lateral (left) and intermediate (right) cerebellar functional zones. Output from the lateral zone goes from the dentate nucleus to the superior cerebellar peduncles, which then decussate to synapse on the contralateral thalamus, which relays to the motor and premotor cortex (e.g., left cerebellum to right thalamus to right motor and premotor cortex). Output from the motor and premotor cortex re-crosses the midline in the pyramidal decussation (e.g., right motor and premotor cortex to left hemicord). The result is that one cerebellar hemisphere influences the ipsilateral side of the body. The intermediate zone output is similarly organized, except that fibers also project to the contralateral red nucleus. The red nucleus projects to the spinal cord via the rubrospinal tract, which also decussates on the way to the cord, upholding the principle that one cerebellar hemisphere influences the ipsilateral cord and body.**

motor and premotor cortex to modulate the motion of the right hand and smoothly guide the right index finger to the nose.

This simplified description highlights a critical clinical fact regarding cerebellar pathology: damage to one side of the cerebellum affects the ipsilateral side of the body. From our example, we see that the left motor cortex "talks to" the right cerebellum, and right cerebellar lesions would, in turn, impact the function of the left motor cortex, which controls the right body. This occurs because of a double decussation of the input–output pathways between the cerebrum and the cerebellum. Information from the cerebrum decussates on the way into the cerebellum in the belly of the pons, and decussates on the way out of the cerebellum in the decussation of the superior cerebellar peduncles.

Similar compensating decussations operate at all levels in the cerebellum to uphold the principle that cerebellar lesions affect the ipsilateral side of the body (Fig. 1.6).

Communication between the cerebellum and the spinal cord is more complex than the cerebrocerebellar circuit described above, but follows similar principles, and a couple of illustrative examples are given (Fig. 1.7). We have already mentioned that climbing fibers (one of the two main inputs to the Purkinje cells) arise in the contralateral inferior olivary nucleus. The spinal tracts that deliver information to the inferior olivary nucleus, however, arise form the hemicord contralateral to the inferior olivary nucleus in which they synapse. Therefore, left spinal hemicord neurons send axons that cross the cord and synapse with the right inferior olivary nucleus, which sends its axons to the left cerebellar hemisphere (Fig. 1.7). Another example is the ventral spinocerebellar tract. As mentioned parenthetically before, this enters the cerebellum via the superior cerebellar peduncle. For concreteness, we follow neurons from the right hemibody. Axons enter the cord and decussate, then ascend in the left ventral spinocerebellar tract, entering the left superior cerebellar peduncle. The axons then decussate once again to synapse in the right cerebellar hemisphere (Fig. 1.7).

Also, some tracts do not decussate at all, such as the dorsal spinocerebellar tract, which enters the cerebellum through the inferior cerebellar peduncle, and synapses ipsilateral to its side of origin in the cord (Fig. 1.7). We can also look at an example of cerebellar efferents, which send information to the spinal cord. A small part of the output of the paravermal zones goes to the cord. It travels via the

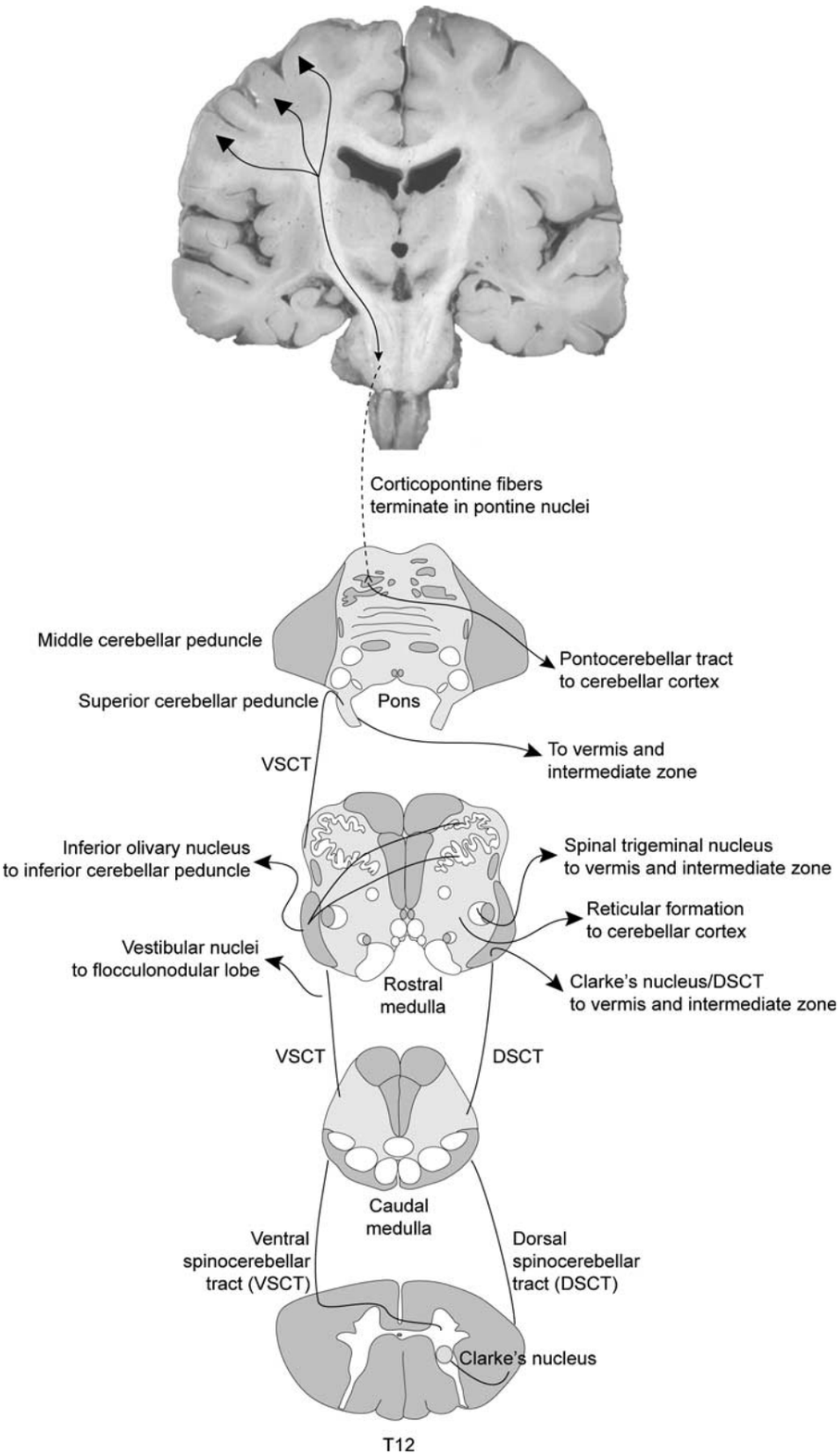


Fig. 1.7. **Schematic of inputs from the cerebral cortex and the spinal cord to the cerebellum. Inputs from the motor and premotor cortex synapse in the pons, and then decussate in the belly of the pons to enter the contralateral cerebellar hemisphere via the middle cerebellar peduncle. Spinal cord inputs are more complex. In the diagram, some fibers from the right hemibody cross the midline in the cord and ascend in the left ventral spinocerebellar tract (VSCT). These fibers enter the left superior cerebellar peduncle, and then decussate to synapse on the right cerebellar hemisphere (right body, left VSCT, right cerebellum). Other fibers, e.g. from the left hemibody, ascend in the ipsilateral cord then decussate to synapse on the contralateral (right) inferior olivary nucleus, which then sends climbing fibers to the contralateral (left) cerebellum (left body, right inferior olivary nucleus, left cerebellar hemisphere). Finally, some fibers, such as the dorsal spinocerebellar tract (DSCT), do not decussate. In the diagram, fibers from the left hemibody ascend in the left DSCT and enter the left cerebellum via the left inferior cerebellar peduncle. In all cases, one cerebellar hemisphere influences the ipsilateral side of the body.**

interposed nucleus and the superior cerebellar peduncle, decussating to synpase on the contralateral red nucleus (Fig. 1.6). The descending rubrospinal (from the red nucleus to the spine) tract decussates again before it enters the cord. Therefore, with regard to communication between the cerebellum and the spinal cord, one side of the cerebellum communicates with the ipsilateral side of the cord, which controls that same side of the body, upholding the principle of cerebellar lesions causing symptoms on the same side of the body.

After this long digression into ipsilaterality, we return to the functional aspects of the lateral zones of the cerebellum. As mentioned previously, the somatotopic maps of the body in the cerebellum have the extremities mapped laterally. Therefore, damage in the lateral zones will cause the so-called neocerebellar syndrome. The most prominent feature here is a peripheral ataxia – an incoordination of voluntary movements characterized by overshooting or undershooting of the target (*dysmetria*), lack of control of the velocity and precise direction of motion (*intention tremor*), difficulty with rapid alternating movements (*dysdiadochokinesia*), and poor timing of different parts of a complex motion (*decomposition of movement*). The complex motor control involved in speaking may be similarly affected, disrupting the normal flow and cadence of speech, causing a cerebellar dysarthria known as *scanning speech*. Other manifestations of the neocerebellar syndrome include hypotonia (part of the function of cerebellar efferents to the motor cortex is to help maintain motor tone) and hyporeflexia. Because of the hypotonia, a limb may continue to swing after a reflex contraction; this is known as a *pendular reflex*.

Vermis and paravermal zones

Both of these zones (except the nodulus of the vermis) receive significant inputs from the spinal cord, and so are together called the *spinocerebellum*. The paravermal zones also receive input from the cerebral cortex. The paravermal zones output through the interposed nucleus and then through the superior cerebellar peduncles. The output decussates and goes predominantly to the contralateral red nucleus, and from there either to the thalamus and then the cortex, or back to the spinal cord through the rubrospinal tract (Fig. 1.8). The paravermal zones work both with the lateral zones in helping to control limb movements and with the vermis.

The vermis receives inputs predominantly from the spinal cord through spinocerebellar tracts. The vermis outputs through the fastigial nuclei, and then to the vestibular nuclei (Fig. 1.9). There are also some direct connections from the vermis to vestibular nuclei bypassing the fastigial nuclei. Since the trunk is primarily represented along the vermis, and since its projections are to the bilateral vestibular nuclei, which function to maintain equilibrium, it is not surprising that damage to the vermis causes central ataxia, manifested by postural instability and gait ataxia. The vermis also functions in concert with the flocculonodular lobe.

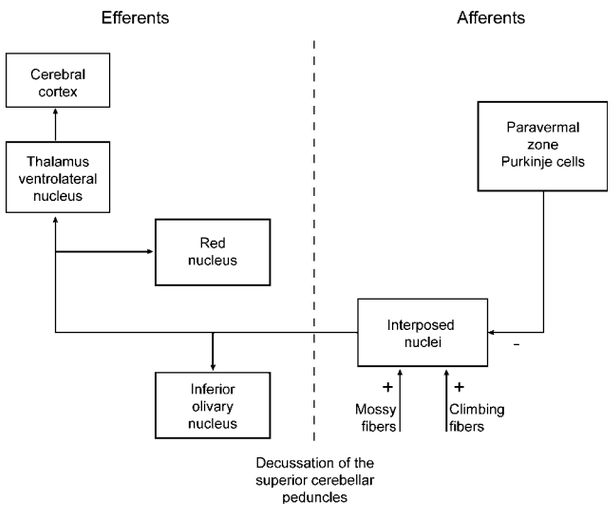


Fig. 1.8. **Schematic diagram showing the inputs (right) and outputs (left) of the paravermal zone of the cerebellum. Outputs of the paravermal zone go through the interposed (globose and emboliform) nucleus. They decussate and go to the contralateral red nucleus, thalamus and cortex, as well as to the inferior olivary nucleus. The red nucleus sends fibers to the spinal cord via the rubrospinal tracts.**

Flocculonodular lobe

This functional zone receives inputs primarily from the vestibular nuclei through the inferior cerebellar peduncles and is therefore known as the *vestibulocerebellum*. Because phylogenetically this zone is the oldest part of the cerebellum, it is sometimes also referred to as the *archicerebellum*. It skips the deep cerebellar nuclei and projects to the vestibular and reticular nuclei (which in turn project to the spinal cord), and to the oculomotor nuclei via the medial longitudinal fasciculus. Damage to the flocculonodular lobe causes the so-called archicerebellar syndrome, characterized by nystagmus and gait and truncal ataxia. Sometimes, there is also a frank sense of disequilibrium, which is noteworthy since sensory manifestations are unusual with cerebellar lesions. The nystagmus is usually horizontal, with the fast component toward the side of the lesion; it is worse when the patient looks toward the side of the lesion.

In an incomplete but pithy summary, then, the lateral zones of the cerebellum (neocerebellum or cerebrocerebellum) receive inputs predominantly from the contralateral cerebral cortex, and output via the dentate nucleus back to that contralateral cerebral cortex via thalamic relays. The intermediate zone (spinocerebellum) is made up of both paravermal cortex and portions of the vermis. The paravermal regions receive inputs from both the spinal cord and the cerebral cortex. They output through the interposed (globose and emboliform) nuclei back to the cerebral cortex via thalamic relays, as well as back to the spinal cord via the red nucleus and the rubrospinal tracts. The vermal portion of the spinocerebellum receives inputs predominantly from the spinal cord, and outputs

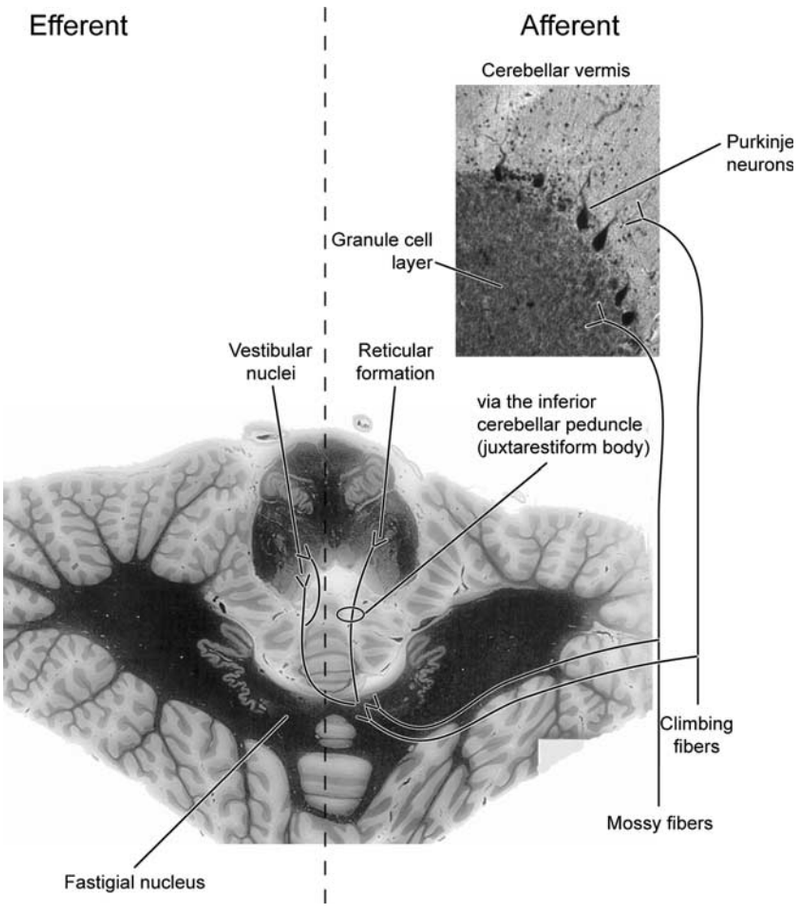


Fig. 1.9. **Inputs and outputs of the cerebellar vermis. Inputs come mainly from the spinal cord through the dorsal and ventral spinocerebellar tracts, as well as by spinoreticular fibers, which synapse on the lateral and paramedian reticular nuclei and then project to the vermis. Outputs of the vermis go predominantly via the fastigial nucleus to the bilateral vestibular nuclei and the reticular formation.**

through the fastigial nucleus to the vestibular nuclei and the reticular formation. The flocculonodular lobe (vestibulocerebellum) receives inputs from the vestibular nuclei predominantly through the inferior cerebellar peduncles. It bypasses the deep cerebellar nuclei and outputs directly to the vestibular and reticular nuclei (which project to the spinal cord) and to the oculomotor nuclei.

Now, let's take some cases!

Case 1.1

56-year-old patient presents with several months of progressive gait ataxia. On examination, the patient walks with a wide-based gait, and has ataxia of the lower extremities on heel-to-shin testing.

A CT examination (Fig. 1.10) is presented below.

What are the findings? What is your differential? What other points of history and physical examination are pertinent?

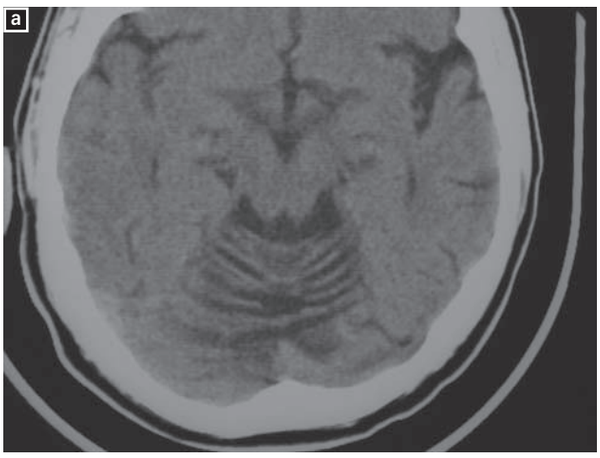
The patient has marked cerebellar atrophy with prominence of the sulci. There is no gross evidence of brainstem atrophy. The cerebellar atrophy is most pronounced in the anterior–superior vermis and paravermal zones (Fig. 1.10(a)). More inferiorly, there is no significant atrophy of the cerebellar hemispheres (Fig. 1.10(b)). The pattern would be consistent with alcohol-induced cerebellar degeneration.

Diagnosis: alcoholic cerebellar degeneration.

A key point in the patient's history would be the extent of ethanol (ETOH) consumption. Other important aspects of the physical examination would center around whether there is significant involvement of the upper limbs, nystagmus, or speech deficits such as dysarthria. These would be unusual with alcohol-induced cerebellar degeneration. In fact, the presence of cerebellar nystagmus or speech pathology should suggest a search for alternative causes of ataxia (however, sometimes there is a concomitant Wernicke's syndrome which has oculomotor abnormalities).

Discuss the underlying pathophysiology of alcohol-induced cerebellar degeneration.

Cerebellar atrophy secondary to alcohol abuse tends to be most prominent in the anterior–superior vermis and paravermal zones. This region corresponds fairly closely with the anterior



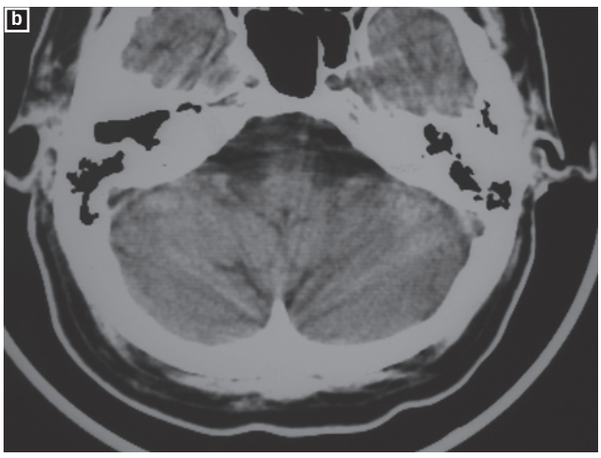


Fig. 1.10. **(a), (b) Axial non-contrast CT images through the cerebellum.**

lobe of the cerebellum. Because the transversely oriented primary fissure occurs so high in the cerebellum, most of the anterior lobe is anterior–superior vermis and paravermal zones. Therefore, as discussed previously, central truncal and gait ataxia would be a prominent feature, with lesser involvement of the upper limbs, and only rarely oculomotor symptoms or cerebellar dysarthria.

The underlying cause of the cerebellar degeneration remains unclear. However, most authorities feel that one of the most likely causes is the thiamine deficiency often associated with alcoholism. This is due to a high degree of correlation, both clinically and pathologically, between alcoholic cerebellar degeneration and cerebellar pathology in Wernicke's syndrome. An interesting clinical aside, however, is that, while there seems to be little sex predilection in Wernicke's when it comes to cerebellar pathology, there is a significant male predilection among alcoholics of alcohol-induced cerebellar degeneration.

Case 1.2

63-year-old male with progressive gait ataxia over several months. Clinical examination reveals a significant truncal, gait and upper extremity ataxia as well as dysarthria.

An MRI is presented (Fig. 1.11).

What are the findings?

There is generalized cerebellar atrophy with prominence of the cerebellar sulci and the fourth ventricle. There is also a suggestion of mild brainstem atrophy involving the basis pontis.

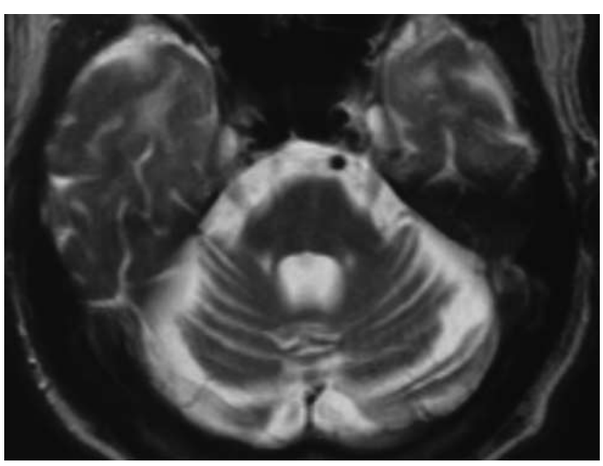


Fig. 1.11. **Axial T2-weighted image of the cerebellum.**

What is your differential diagnosis? What additional clinical history might be useful?

There is a long differential for cerebellar atrophy and ataxia, which will be discussed as part of this case and the subsequent case. Two critical points, however, are worth making now:

(1) The findings, which include dysarthria and upper limb ataxia, would make alcoholic cerebellar degeneration an unlikely diagnosis, despite its ubiquity. However, an ETOH history is always important. Our patient has no history of ETOH abuse, but has an 80-pack/year smoking history.
(2) In patients over the age of 40 with subacute (as opposed to slow or acute) cerebellar syndromes, paraneoplastic cerebellar degeneration probably accounts for 50 percent or more of the cases. It is definitely an under-recognized entity, and you should think about underlying, possibly occult, neoplasia.

Look at the accompanying chest CT (Fig. 1.12). What are the findings and what is your diagnosis?

You are probably thinking that this is highly unfair – even egregious – to be asked to make diagnoses from a chest CT in a neuroradiology book. Sorry. Moving on, the chest CT shows diffuse middle mediastinal and hilar adenopathy with central necrosis. Given the heavy smoking history, this suggests small cell lung carcinoma.

Diagnosis

Paraneoplastic cerebellar degeneration (PCD); small cell lung carcinoma.

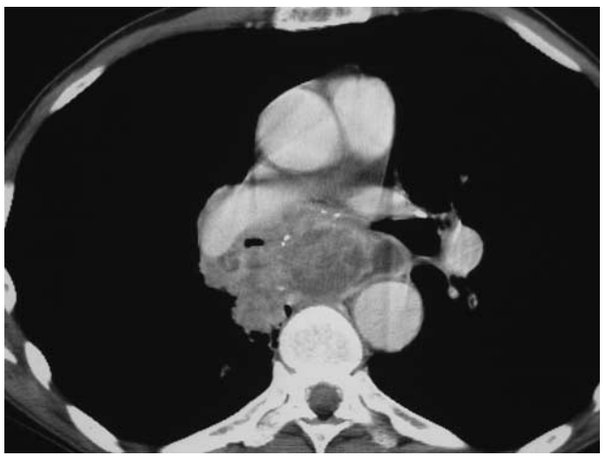


Fig. 1.12. **Contrast CT of the chest.**

Discuss the pathology of paraneoplastic cerebellar degeneration.

When faced with a patient with known cancer and cerebellar ataxia, the leading differential possibility is metastatic disease to the cerebellum. However, paraneoplastic cerebellar degeneration should be considered if there are no metastases visible, and "in the appropriate clinical setting." This phrase is often an irritating hedge, but in this case, it is actually meaningful. There is a definite epidemiology or "appropriate clinical setting" to PCD. Interesting references in this regard are Peterson *et al.* (1992) and Shams'ili *et al.* (2003).

PCD with detectable antibodies

About half of the cases diagnosed as PCD have anti-neuronal antibodies in the serum and cerebrospinal fluid. The antibodies differ based on the underlying malignancy, but they are not seen in other cerebellar disease, so their detection is useful, as it may point to an occult neoplasm, or help confirm the diagnosis of paraneoplastic cerebellar degeneration.

The most common antibody is called anti-Yo. It is directed against the Purkinje cells and can be detected by Western blot testing. It is seen only in women. About half of the cases of anti-Yo associated PCD are due to ovarian carcinoma, while the other half are mainly due to breast carcinoma or other gynecological malignancies.

Other cancers in the PCD with detectable antibody group include Hodgkin's lymphoma, which may be associated with paraneoplastic cerebellar degeneration. In about one-third of the cases of Hodgkin's with associated PCD, there are anti-Purkinje cell antibodies; these are different from anti-Yo. They have a different cytoplasmic staining pattern (diffuse versus granular, as in anti-Yo), and are not detectable on Western blot testing.

Patients with small cell lung cancer sometimes have antibodies against various cells in the central nervous system, known as anti-Hu antibodies. These are not specific to the cerebellum and may be seen in such syndromes as paraneoplastic limbic encephalitis. However, sometimes patients with small cell lung cancer present with isolated PCD.

According to Shams'ili *et al.*, there are nine specific neuronal antibodies associated with PCD, including anti-Yo, anti-Hu, anti-Tr, anti-Ri, and anti-mGluR1.

PCD without detectable antibodies

As already mentioned, this group makes up about one-half of the total cases of PCD. About two-thirds of patients with Hodgkin's lymphoma and associated paraneoplastic cerebellar degeneration are in this group. Other than Hodgkin's disease, the main cancers in this group are lung and breast.

While paraneoplastic cerebellar degeneration is probably underrecognized, its prevalence in lung and ovarian cancer patients is low, probably less than 5 percent. MRI findings may be absent until late in the disease, and the cerebellar symptoms predate the diagnosis of malignancy in a significant proportion of the cases. In fact, in the paper of Peterson *et al.*, cerebellar symptoms preceded the diagnosis of cancer in 34 out of 52 patients, while in the paper of Shams'ili *et al.*, symptoms predated the clinical diagnosis of tumor in 26 out of 42 patients. MRI findings, when present, tend to be diffuse cerebellar atrophy, which may be associated with mild brainstem atrophy as well.

Clearly, a specific diagnosis of PCD simply from a history of cerebellar ataxia and an MRI showing cerebellar atrophy would be difficult, since there is a broad differential for this constellation. An excellent classification of ataxias was introduced by Harding in the early 1980s:

I. Hereditary ataxias

A. Autosomal recessive ataxias

This includes such ataxias as Friedreich's Ataxia, Ataxia Telangiectasia, Congenital Ataxias, and Early-onset Cerebellar Ataxia. It is noted that significant recent progress has been made in uncovering the genetic basis of many of these syndromes, such as the X25 gene on chromosome 19 in Friedreich's ataxia or the phosphatidyl inositol kinase mutation (11q22–23) in Ataxia Telangiectasia.

A quick clinical note regarding Friedreich's ataxia is that it is primarily a spinal degeneration with only occasional involvement of the cerebellum. Therefore, significant cerebellar atrophy is not usually seen on MRI. This is mentioned because residents usually say Friedreich's ataxia first when seeing a case of profound cerebellar atrophy in a young person. Early-onset Cerebellar Ataxia (EOCA) is another autosomal recessive hereditary ataxia. It does show significant cerebellar atrophy. It may be distinguished from Friedreich's ataxia in that patients with Friedreich's ataxia usually lose their tendon reflexes, while patients with EOCA have retained tendon reflexes. Friedreich's ataxia patients also often have other abnormalities, such as cardiomyopathy.

B. Autosomal dominant cerebellar ataxias

This category includes spinocerebellar ataxias types 1 to 6. (SCA1–SCA6) and such entities as the episodic ataxias.

The spinocerebellar ataxias are further subdivided into those without and those with retinal degeneration. The chromosomal disease loci for various SCA syndromes have been determined (SCA1-6p; SCA2-14q; etc.).

The responsible mutation is often a CAG repeat expansion. The various genetic and clinical differences between these syndromes are beyond the scope of this work. However, the degree of cerebellar atrophy on imaging is different among the syndromes, being very profound in SCA2 for example, but quite mild in SCA3, also known as Machado–Joseph syndrome.