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section 24 Neurological disorders 5976 Rippling muscle disease due to autosomal-dominant caveolin-3 mu- tations can give rise to a clinically similar picture, but differs in elec- tromyographic silence, despite muscle movement. Myorhythmia Myorhythmia is defined as repetitive, rhythmic, slow (1–4 Hz) movement affecting chiefly cranial and limb muscles. Oculo- masticatory myorhythmia is characterized by synchronous 2 Hz vergence spasms of the eyes sometimes with contraction of the mas- seter with the palate and diaphragm also being involved. It is virtu- ally pathognomonic of Whipple's disease, a rare, systemic infectious disease caused by the bacterium Tropheryma whipplei and merits mention as a treatable disorder. FURTHER READING General Donaldson I, et al. (2012). Marsden's book of movement disorders. Oxford University Press, Oxford. Edwards M, et al. (2015). Parkinson's disease and other movement disor ders. Oxford University Press, Oxford. Chorea Gövert F, Schneider SA (2013). Huntington's disease and Huntington's disease-like syndromes: an overview. Curr Opin Neurol, 26, 420–7. Dystonia Balint B, Bhatia KP (2014). Dystonia: an update on phenomenology, classification, pathogenesis and treatment. Curr Opin Neurol, 27, 468–76. Myoclonus Kojovic M, Cordivari C, Bhatia K (2011). Myoclonic disorders: a prac- tical approach for diagnosis and treatment. Ther Adv Neurol Disord, 4, 47–62. Zutt R, et al. (2015). A novel diagnostic approach to patients with myo- clonus. Nat Rev Neurol, 11, 687–97. Tremor Gövert F, Deuschl G (2015). Tremor entities and their classifica- tion: an update. Curr Opin Neurol, 28, 393–9. Tics and Tourette's syndrome Ganos C, Martino D (2015). Tics and tourette syndrome. Neurol Clin, 33, 115–36. Paroxysmal dyskinesia Erro R, Sheerin UM, Bhatia KP (2014). Paroxysmal dyskinesias re- visited: a review of 500 genetically proven cases and a new classifi- cation. Mov Disord, 29, 1108–16. Stiff person syndrome Meinck HM, Thompson PD (2002). Stiff man syndrome and related conditions. Mov Disord, 17, 853–66. Functional movement disorders Edwards MJ, Bhatia KP (2012). Functional (psychogenic) movement disorders: merging mind and brain. Lancet Neurol, 11, 250–60. Morgante F, Edwards MJ, Espay AJ (2013). Psychogenic movement disorders. Continuum (Minneap Minn), 19(5 Movement Disorders), 1383–96. Drug-induced movement disorders Mehta SH, Morgan JC, Sethi KD (2015). Drug-induced movement disorders. Neurol Clin, 33, 153–74. 24.7.4 Ataxic disorders Nicholas Wood ESSENTIALS Ataxia is a feature of disorders of the cerebellum and its connections. It may be found in a large

range of neurological conditions, in some of which it is the principal or main feature, but clinical assessment is complicated by the fact that few ataxic patients have disease re- stricted to the cerebellum alone. Clinical features Symptoms—common presenting complaints are (1) gait unsteadiness— particularly with lesions of the vermis; (2) limb incoordination and tremor—particularly with lesions of the cerebellar hemisphere; (3) slur- ring of speech; and (4) visual and oculomotor symptoms, although these are rare in pure cerebellar disease. Signs—these include (1) a broad-based gait with a poor turn; (2) scanning dysarthria; (3) limb ataxia—manifest as dysmetria and dysdiadochokinesis; (4) intention tremor; (5) abnormal eye movements. Key points in differential diagnosis—(1) age of onset—early-onset is before 20–25 years; (2) rate of onset and the nature of the pro- gression of the illness; (3) other features of neurological involvement, which enables differentiation of the 'pure' ataxias from the 'compli- cated' ataxias. Investigation and treatment—high-resolution imaging, genetic testing and other investigative tools enable a diagnosis to be made in over 50% of cases. The mainstay of management is supportive: there are no drugs that help cerebellar balance problems, but active engagement in physiotherapy can help to lessen the impact of the physical disorder. Particular causes of ataxia Ataxias with early-onset—(1) acute and subacute ataxias with onset in childhood—should raise the possibility of infectious, para-infectious or vascular conditions; (2) chronic progressive ataxias of early-onset— very often genetic in aetiology, typically autosomal recessive, with the commonest cause being Friedreich's ataxia; a clear molecular genetic diagnosis can be established in most cases. Chronic progressive ataxia—causes include (1) genetic—with in- heritance typically being autosomal dominant; (2) chronic alcohol abuse—probably the most common cause of progressive cerebellar degeneration in adults; (3) deficiency disorders (e.g. vitamin E); (4) toxic agents—drugs (e.g. phenytoin), solvents, and heavy metals; (5) structural lesions in the posterior fossa; and (6) other (e.g. Wilson's disease, other metabolic disorders). No cause can be found in many cases, labelled as 'idiopathic late-onset cerebellar ataxia', with the commonest pattern recognized being that of multiple system at- rophy, where there is typically ataxia complicated by autonomic failure and (in some cases) Parkinsonism. Rapid, subacute onset ataxia—should always raise the possibility of paraneoplastic or other inflammatory conditions. Acute ataxia—the two main causes are (1) cerebellar haemorrhage— usually associated with headache, vertigo, vomiting, altered conscious- ness and neck stiffness; and (2) cerebellar infarction—in which cerebellar signs are usually combined with signs of brainstem ischaemia.

24.7.4 Ataxic disorders 5977 Introduction The term ataxia derived from the Greek means 'irregularity' or 'disorderliness'. Unsteadiness can result from several causes, including poor vision, impairment of postural reflexes, or due to a deficiency of sensory input (i.e. sensory ataxia). This chapter focuses on the symptoms, signs, and the pathological and clin- ical features of the disorders of the cerebellum (and its connec- tions). There are two basic clinical rules that can be applied: (1) lesions of the vermis generally cause ataxia of midline struc- ture (i.e. truncal and gait ataxia); (2) output from the cerebellar hemisphere is to the contralateral cerebral hemisphere, which provides output to the contralateral limbs, therefore cerebellar hemisphere lesions are ipsilateral. It should however be noted that, clinical assessment is complicated by the fact that many ataxic patients have additional pathology in the brain stem, spinal cord, or elsewhere. Symptoms of ataxic disorders The patient history is extremely important and the most common presenting complaints are of gait unsteadiness or slurring of speech. On direct enquiry many patients will admit to receiving 'jokes' or accusations of being drunk by acquaintances. The joke tends to wear thin. Some refer to 'giddiness' or 'dizziness' when they really mean unsteadiness of

gait without associated vertigo or lightheadedness. A particular note in the history of the age, speed of onset, and devel- opment of other features may provide important aetiological clues. Rate of progress and any precipitating or relieving factors should also be noted. A range of genetic tests is now available, and a detailed family history is paramount. Disturbances of gait This is the most frequent presenting feature in ataxic disorders. Patients may report an inability to walk in a straight line and a tendency to bump into things. A history of it being worse in the dark may suggest a sensory ataxia and involvement of the proprio- ceptive pathways. Sudden changes of direction are particularly dif- ficult and problems turning may be reported. The duration of the gait disturbance should be established and it is worth asking about early motor milestones and athletic ability at school that may bring out a much longer history than previously appreciated. Collateral history should be sought, especially if an insidious onset is sus- pected, as this may be difficult for a patient to report. A question as to diurnal variation, particularly a history of morning unsteadi- ness that wears off later in the day, often associated with morning headache, may suggest raised intracranial pressure even if exam- ination is normal. Limb incoordination and tremor Clumsiness of the arms is often noted as the illness progresses. Generally, a tremor that is worse on action is reported and as this worsens patients notice clumsiness carrying objects and deteri- oration of their handwriting. Marked tremor is more common in multiple sclerosis than in degenerative disease. Disturbance to the midline structures may result in titubation and this, in combination with action tremor in the upper limbs, and little in the way of gait disturbance, should raise the suspicion of Wilson’s disease. Dysarthria This may be noted by friends and relatives before the patient. Classically described as having a staccato quality, it is a useful symptom or sign as it points against a purely sensory ataxia. It is also worth listening to the speech as many patients have a dysarthria with cerebellar features mixed with spastic or dysphonic elements. Visual and ocular motor symptoms Visual symptoms are relatively rare in pure cerebellar disease and, if present, are more often associated with brain stem disturbance, espe- cially episodic or persistent diplopia associated with ataxia. Vertical oscillopsia suggests downbeat nystagmus and a structural foramen magnum lesion should be suspected. Acute or subacute oscillopsia, with chaotic involuntary eye movements, may be mentioned in the history of patients with viral cerebellitis, paraneoplastic cerebellar degeneration, and the dancing eyes syndrome (opsoclonus). There are some very rare degenerative ataxias with gradual visual loss, due to either optic neuropathy or retinopathy. Other symptoms Details of any headache or vomiting should be sought. Its presence may suggest a posterior fossa mass lesion. If the history is acute then a vascular event, in particular a cerebellar haemorrhage should be considered. Whereas in cases with a more protracted course a tu- mour becomes more likely. Ancillary signs of infection should raise the possibility of an abscess. Intermittent symptoms could indicate the presence of an episodic ataxia (see later) or, if found in the pres- ence of malaise and fever, raise the possibility of posterior fossa cysticercosis. A history of vertigo is more suggestive of neoplastic, inflammatory, and vascular disease rather than the more slowly pro- gressive degenerative processes. Direct questioning should cover the urinary system, skeletal de- formities, cardiac disease, and assessment of cognitive abilities since many ataxias can be associated with disease in other systems (see Table 24.7.4.1). A detailed inquiry of drug ingestion (for both medical and recre- ational purposes, including alcohol) and occupational exposure is also required. Signs of cerebellar disease It is generally good practice in neurology to greet the patient in the waiting room; observe them rising from a chair mobilizing to the consulting room, shaking hands, and hearing their speech. In the case of the ataxic patient this sequence provides much of the information one needs to characterize the disease. Gait and posture A patient may demonstrate a broad-based gait, with a poor turn and there is often a lurching quality to the

overall sequence. More de- tailed assessment of mild gait ataxia may be obtained by asking the patient to tandem walk (heel-toe). Asking the patient to stand still may reveal the broad base and also permits the assessment of pro- prioception via Romberg's test.

section 24 Neurological disorders 5978 Speech It is often stated that cerebellar speech is very distinctive with an ex- plosive quality, so-called scanning dysarthria. Although when this is heard it is characteristic, frequently a combination of cerebellar and spastic features may be heard. Additional signs such as a slow- moving tongue and brisk jaw jerk support the latter. Muscle tone Some textbooks state firmly that cerebellar disease gives rise to hypotonia, and some even include it within the symptoms. Not only do patients never complain of hypotonia, but this is rarely detectable clinically in symmetrical slowly progressive or chronic disorders. Pendular knee jerks are also difficult to detect without the eye of faith and many patients with 'cerebellar' ataxic disorders have dis- ease of the spinal cord, peripheral nerves, or both, which compli- cates the clinical picture. Limb ataxia Limb ataxia is usually assessed by looking for evidence of dysmetria and dysdiadochokinesis. Dysmetria refers to errors in the range and force of movement resulting in an erratic, jerky movement which may under- or overshoot the target. This is most simply assessed using finger nose and heel shin tests. Dysdiadochokinesis is demon- strated by asking the patient to tap one hand on the other, alternately pronating and supinating the tapping hand, or rapidly opening and closing the fist. In addition, the tapping out of simple rhythms (with the hand or foot) is also useful for assessing both the rhythmicity and force of the tap. Traditionally testing of coordination is undertaken after the motor and sensory tests as the presence of weakness or sensory loss can confuse the picture. It should be remembered that there is a natural asymmetry in cerebellar function, with better performance, particu- larly for rapid alternating movements, in the dominant limb. About 40% of patients with vermis lesions do not have limb ataxia but have prominent gait ataxia. Tremor Intention tremor is present if a rhythmical side-to-side oscillation is seen on finger-nose testing. A combination of gross intention tremor and a postural component is often called rubral or red nu- cleus tremor, although peduncular tremor is probably a more ac- curate label. It is most commonly seen in multiple sclerosis and Table 24.7.4.1 Differential diagnosis of ataxic disorders: associated general physical signs Short stature Mitochondrial encephalomyopathy Ataxia telangiectasia Sjögren–Larsson syndrome Cockayne syndrome Hypogonadism Recessive ataxia with hypogonadism, ataxia telangiectasia, Sjögren–Larsson syndrome, mitochondrial encephalomyopathy, adreno-leukomyeloneuropathy Skeletal deformity Friedreich's ataxia, Sjögren–Larsson syndrome, many other early-onset inherited ataxias, hereditary motor, and sensory neuropathy Immunodeficiency Ataxia telangiectasia, multiple carboxylase deficiencies Malnutrition Vitamin E deficiency, alcoholic cerebellar degeneration Hair Argininosuccinicaciduria—brittle Giant axonal neuropathy—tight curls Thallium poisoning, hypothyroidism, adrenoleukomyeloneuropathy - Loss - Foramen magnum lesions - Low hairline Skin Telangiectases, particularly conjunctiva, nose,
ears, flexures Extreme light sensitivity, tumours Pellagra-type rash Tendinous swellings Dry skin Pigmentation Ataxia telangiectasia Xeroderma pigmentosum Hartnup's disease Cholestanolosis Hypothyroidism, Refsum's disease Cockayne's syndrome Adrenoleukomyeloneuropathy Eyes Kayser-Fleischer rings Ataxia telangiectasia Cataract Telangiectasia Aniridia Wilson's disease Retinal angiomas in von-Hippel-Lindau disease Congenital rubella, cholestanolosis, Sjögren–Larsson syndrome Gillespie syndrome Fever Abscess, viral cerebellitis, cysticercosis, dominant periodic ataxia, intermittent metabolic ataxias Haemorrhage, infarction, demyelination, posterior fossa mass lesions, intermittent metabolic ataxias Hepatosplenomegaly Niemann–Pick disease type C,

some childhood metabolic ataxias, Wilson’s disease, alcoholic cerebellar degeneration Heart disease Friedreich’s ataxia Cardiomegaly, murmurs, arrhythmias, late heart failure, abnormal ECG Mitochondrial encephalomyopathy Conduction defects

24.7.4 Ataxic disorders 5979 occasionally in late-onset degenerative ataxias. A nodding head tremor (titubation) with a frequency of 3–4 Hz may be seen with midline cerebellar disease. Eye movements This assessment is really useful in patients with possible cerebellar dysfunction as it is extremely uncommon to find patients with cere- bellar disease with a completely blameless oculomotor examination. However, one may need to search quite hard for the abnormal signs. In the primary position one should spend a moment looking for the presence of square wave jerks; these are inappropriate saccades that disrupt fixation and are followed by a corrective saccade within 200 msec. In practice this appears as a quick ‘shuffle’ on and off the point of fixation. Assessment of pursuit usually reveals jerkiness as a result of saccadic intrusions. Additional isolated or multiple lesions of the third, fourth, or sixth cranial nerves suggests brain stem path- ology. Examination of the saccadic system permits an assessment of saccadic initiation, velocity, and accuracy. Also the presence of an internuclear ophthalmoplegia may be found, indicated by slow- ness of an adducting eye, and suggesting a diagnosis of multiple sclerosis, but can also rarely be associated with some degenerative ataxias. The vestibulo-ocular reflex (dolls head manoeuvre) should then be examined to look for any supranuclear component. An in- ability to suppress the vestibulo-ocular reflex is evidence of path- ology involving the vestibulocerebellum. Acute or subacute presentation of almost any of the aforemen- tioned eye movements especially if associated with alcohol abuse or vomiting, raises the possibility of Wernicke’s encephalopathy and re- quires urgent treatment with thiamine. Gaze-evoked nystagmus is the most common type of nystagmus associated with cerebellar disease; eccentric gaze cannot be main- tained, and the slow phase of the nystagmus is toward the primary position, with rapid corrective movements. Apart from down beat nystagmus, which may indicate a foramen magnum lesion, gaze- evoked nystagmus is of limited localization value in most forms of ataxia. Positional nystagmus in a patient with vertigo and unsteadiness should be attributed to benign labyrinthine disease only if it is tran- sient, torsional, and fatigable; if it does not have these features, a pos- terior fossa lesion should be suspected. Other neurological signs and general examination As the causes of ataxia are numerous, a large variety of other neuro- logical and general physical signs may be found on examination. The range of these and their possible diagnostic significance is shown in Table 24.7.4.1. Investigations This is necessarily a brief overview of a complex area. Imaging Imaging has had a huge impact on clinical neuroscience. For the ataxias it helps identify structural lesions (e.g. tumours, vascular events, and demyelination). It may also confirm the clinical impres- sion of a degenerative process with the presence of atrophy. The use of magnetic resonance imaging (MRI) for monitoring cerebellar disease progression is still limited and generally not clinically useful as there is a poor correlation between severity of symptoms and de- gree of atrophy. However, there are occasionally distinctive imaging features (e.g. molar tooth sign in Joubert’s syndrome; thinning of corpus callosum in SPG11 and autosomal recessive spastic ataxia of Charlevoix– Sagueney, or ARSACS). Genetics There are some gene tests that are widely available (e.g. FRDA and some of the SCAs; see Tables 24.7.4.4 and 24.7.4.5a). Several diag- nostic labs are now offering a broader range of tests on so-called gene panels and this will rapidly be followed by the clinical appli- cation of whole exome and whole genome sequencing approaches. This will provide much greater clarity as to potential genetic causes underlying the myriad genetic ataxias. Quantifying the anatomy Many of the conditions discussed in this chapter are complex and this author has a low threshold

for requesting further investigations to help identify and quantify other deficits. This includes nerve con- duction studies (e.g. the presence of a demyelinating neuropathy ra- ther than axonal can help in dissecting the differential diagnosis); a sensory neuronopathy points to a different group of disorders compared to a generalized neuropathy and so on. A formal neuro- psychological assessment can also be very useful. Disorders of the cerebellum There are numerous pathological processes that can affect cere- bellar function. Some of them, such as multiple sclerosis and neo- plasia are discussed elsewhere (Chapter 24.10.2). In this section I have broadly attempted to classify these using age at onset and time course of the process. Developmental disorders The cerebellum has a long developmental period and is not fully ma- ture until about 18 months of age. It is therefore susceptible to many insults, including intrauterine infections, ischaemic damage, toxins, and genetically determined syndromes (see Table 24.7.4.2). Some of these developmental anomalies, such as dysgenesis or agenesis of the vermis, the cerebellar hemispheres, or parts of the brain stem, give rise to congenital ataxia. These are nonprogressive disorders, and in most cases, coordination improves somewhat with age. Cerebellar dysfunction in an infant or young child may be over- looked, as it often gives rise to relatively nonspecific abnormal motor development. Later there is nystagmus, obvious incoordination on reaching for objects and truncal ataxia when first attempting to sit. Associated mental retardation is common but unhelpful diagnostic- ally as there is a long differential diagnosis. Ataxia of acute or subacute onset Cerebellar ataxia with extremely acute onset has two main causes: cerebellar haemorrhage (usually associated with headache, vertigo, vomiting, altered consciousness and neck stiffness), and cerebellar infarction (in which cerebellar signs are usually com- bined with signs of brain stem ischaemia, and the presentation may

 mimic that of haemorrhage). Imaging can help with the differential diagnosis. Subacute, reversible ataxia may occur as a result of viral infection in children 2–10 years of age. There is usually pyrexia, limb, and gait ataxia, and dysarthria developing over hours or days. Recovery oc- curs over a period of weeks and is usually complete but can take up to 6 months. In older patients, the possibility of a postinfectious enceph- alomyelitis, particularly that related to varicella infection, should be considered. The postinfectious Miller Fisher variant of the Guillain– Barré syndrome may present with a triad that includes subacute ataxia, areflexia, and ophthalmoplegia. Nerve conduction studies and cerebrospinal fluid (CSF) examination may be helpful, but the former are often normal. Other infective agents are shown in Table 24.7.4.3. Viral titres and CSF examination may be helpful although serological evidence of viral infection may be difficult to establish. Other causes of subacute ataxia include paraneoplastic dis- orders (see Chapter 24.23), hydrocephalus, foramen magnum compression, posterior fossa tumour (primary or secondary), ab- scess, or parasitic infection in any age group. Several important toxins and drugs also need to be considered including thallium, lead, barbiturates, phenytoin, piperazine, alcohol, solvents, and antineoplastic drugs. Vascular disorders of the cerebellum Cerebrovascular disease is dealt with in detail in Chapter 24.10.1. Transient ischaemic attacks involving the vascular supply to the cerebellum rarely produce a pure ataxic syndrome and usually there are associated symptoms of brain stem dysfunction. Cerebellar in- farction (from embolus or, more commonly, vertebrobasilar oc- clusive disease) and haemorrhage (usually on a background of hypertension or, less commonly, secondary to a vascular malforma- tion or tumour) are relatively rare. Imaging is often necessary for early diagnosis as the later the diagnosis the worse the prognosis. Surgical intervention to relieve pressure may be required. Ataxia with an episodic course These attacks may be considered bizarre and some patients are misdiagnosed as nonorganic; however, a good history

can usually distinguish between the main causes (in order of approximate fre- quency): drug ingestion, multiple sclerosis, transient vertebrobasilar ischaemic attacks, foramen magnum compression, intermit- tent obstruction of the ventricular system due to a colloid cyst or cysticercosis, and a growing list of inherited episodic ataxias (n >8 at the time of writing). Autosomal dominant episodic ataxia is characterized by child- hood or adolescent onset of attacks of ataxia, dysarthria, vertigo, and nystagmus. Not all patients have affected relatives. There are at least two forms of this disorder: Episodic ataxia 1 (EA1), due to mutations in a potassium channel Kv1.1, is typified by brief attacks (minutes and occasionally hours) and clinically and electrophysio- logically myokymia may be seen. These patients may benefit from acetazolamide or phenytoin. Patients tend to be neurologically normal between the attacks. In episodic ataxia 2 (EA2) the attacks tend to be longer, lasting hours or even days. They are usually associated with vertigo and con- sequent nausea and vomiting. They tend to be more severe in child- hood with associated drowsiness, headache, and fever. Although when the disease first begins the patients are well, between attacks an interictal nystagmus can be seen. As the disease progresses a slow de- terioration in the ataxia is seen. MRI may reveal cerebellar atrophy. These patients tend to respond better to acetazolamide therapy than patients with EA1. However, increasingly other varieties of episodic ataxia are being recognized, see Table 24.7.4.5a. In children and young adults a metabolic disorder should be sus- pected, particularly defects of the urea cycle, aminoacidurias, Leigh's syndrome, and mitochondrial encephalomyopathies. Screening in- vestigations include serum ammonia, pyruvate, lactate and amino acids, and urinary amino acids. Table 24.7.4.2 Congenital inherited ataxic disorders Syndrome Genetics Additional features Joubert's syndrome Autosomal recessive AHI1 gene NPHP1 gene CEP290 Plus others with established and distinct loci With episodic hyperpnoea, abnormal eye movements, and mental retardation Gillespie's syndrome Autosomal recessive PAX6 With mental retardation and partial aniridia Congenital ataxia with mental retardation and spasticity Autosomal recessive, autosomal dominant, and X-linked NYS1-6p NYS2—X-linked, and others Includes pontoneocerebellar and granule cell hypoplasia Disequilibrium syndrome Autosomal recessive Paine's syndrome X-linked recessive ataxia—no gene identified With spasticity, mental retardation, and microcephaly Table 24.7.4.3 Infections causing cerebellar disease Viruses Others Echo Mycoplasma pneumoniae Coxsackie groups A and B Legionella pneumoniae Herpes simplex Lyme disease Poliovirus Toxoplasma gondii Epstein–Barr Typhoid fever Varicella Plasmodium falciparum Congenital rubella Tick paralysis Prion disease

24.7.4 Ataxic disorders 5981 Ataxia with a chronic progressive course Chronic alcohol abuse is probably the most common cause of pro- gressive cerebellar degeneration in adults. Thiamine deficiency is the main (but not sole) explanation for the chronic progressive cere- bellar syndrome found in alcoholics. Patients with this syndrome are frequently malnourished. Ataxia may develop during periods of abstinence, and identical cerebellar degeneration has been observed in nonalcoholic patients with severe malnutrition. Cerebellar ataxia is common in the Wernicke–Korsakoff syndrome, and the patho- logical features of both this syndrome and cerebellar degeneration are frequently found together. With administration of thiamine some improvement may occur in early cases of alcoholic cerebellar degeneration but, if the patient is already chairbound, the response to treatment is limited. There are other deficiency disorders that can give rise to a progressive ataxia. There is a rare syndrome associated with zinc deficiency that responds to oral replacement therapy. Deficiency of vitamin E, either genetic (e.g. isolated vitamin E deficiency due to mutations in α-tocopherol transfer protein, or abetalipoproteinaemia) or acquired,

may produce a progressive ataxia. Establishing the diagnosis of vitamin E deficiency is im- portant as treatment with vitamin E may prevent progression of the neurological syndrome and can, in rare circumstances, lead to some improvement. There are several toxic agents that can produce progressive cere- bellar dysfunction, including pharmaceutical products, solvents, and heavy metals. The most common cause of a cerebellar syndrome due to drug toxicity in neurological practice is that associated with anti- convulsant medication, particularly phenytoin. Transient ataxia, dys- arthria, and nystagmus usually develop when serum concentrations of phenytoin, carbamazepine, or barbiturates are above the thera- peutic range, and remit when they return to the therapeutic range. Chronic phenytoin toxicity may cause persistent cerebellar dysfunc- tion, and this is associated pathologically with loss of Purkinje cells. A persistent cerebellar deficit, with dysarthria and limb and gait ataxia and cerebellar atrophy on imaging, has also been described as a sequel to the acute encephalopathy of lithium toxicity that is usually precipitated by fever or starvation. Recreational or accidental exposure to several solvents, including carbon tetrachloride and toluene, causes cerebellar ataxia along with other neurological problems, including psychosis, cognitive impair- ment, and pyramidal signs in the case of toluene. The neurological deficit is potentially reversible but may persist after prolonged ex- posure in solvent abusers. Exposure to heavy metals, including in- organic mercury, lead, and thallium, can also produce cerebellar damage. Structural lesions such as posterior fossa tumours, foramen magnum compression, or hydrocephalus must be excluded by imaging studies. Tumours which may involve the posterior fossa in- clude: astrocytoma, ependymoma, haemangioblastoma, and cranial nerve neuromas. Paraneoplastic cerebellar degeneration related to carcinomas of the lung or ovary usually follows a subacute course, with pa- tients losing the ability to walk within months of onset. A variety of antineuronal antibodies may be found in these patients and help to confirm the diagnosis. Approximately half of patients with paraneoplastic cerebellar degeneration have demonstrable anti- bodies directed against neurons in serum and CSF. A search for the underlying malignancy should then be undertaken involving imaging and analysis of tumour markers. Presentation with ataxia precedes diagnosis of the malignancy in 70% of cases and is usu- ally subacute, progressing to severe disability over several months or even weeks and then arresting. Onset may be acute and is sometimes accompanied by vertigo, mimicking a vascular event. There is severe truncal, gait and limb ataxia, and dysarthria. Opsoclonus may be combined with myoclonus, producing a disorder in adults similar to the dancing eyes syndrome of childhood. The latter is sometimes associated with neuroblastoma. There is currently no proof that im- munosuppressant therapy or plasma exchange improves outlook but there are anecdotal reports of some improvement or stabiliza- tion following removal of the primary tumour. The best method of screening for the underlying malignancy is debated but standard MRI imaging may be complemented by whole body positron emis- sion tomography (PET) technology. Searching for primary tumour markers may also be useful. Rarely, infectious agents can cause slowly progressive ataxia (see Table 24.7.4.3), these include the chronic panencephalitis of con- genital rubella infection in children and, in adults, Creutzfeldt– Jakob disease, particularly the iatrogenic form, should be considered. A specific enquiry regarding potential risk factor ex- posure should be sought, especially growth hormone replacement, although following introduction of stringent controls on source material this has become extremely rare. Multiple sclerosis only exceptionally presents as an isolated chronic progressive cerebellar syndrome. Some conditions that are not generally considered primarily as ataxic disorders may present with clumsiness, tremor, or definite cerebellar signs, particularly in childhood or adolescence. These include Wilson’s disease and several inherited neuropathies, such as Charcot-Marie-Tooth disease. Although intention and postural tremor are quite frequent in the

demyelinating type of Charcot- Marie-Tooth (type I), dysarthria and pyramidal signs do not occur. Other chronic demyelinating neuropathies, such as chronic inflam- matory and paraproteinemic neuropathies and Refsum's disease, may give rise to prominent tremor and ataxia; the same applies to giant axonal neuropathy. Superficial siderosis is a rare disorder that causes slowly progres- sive cerebellar ataxia, mainly of gait, and sensorineural deafness, often combined with spasticity, brisk reflexes, and extensor plantar responses. The diagnosis may not be suspected clinically, but the neuroradiological abnormalities are striking, MRI showing a black rim of haemosiderin around the posterior fossa structures and spinal cord, and less often the cerebral hemispheres, on T2-weighted im- ages. Superficial siderosis is most commonly secondary to chronic leaking of blood into the subarachnoid space. Treatment relies on identifying the source of bleeding; chelation therapy does not appear to be effective. After excluding acquired causes of ataxic disorders, there re- mains a considerable number of patients with degenerative ataxias, not all of which are overtly genetically determined. The inherited ataxias can largely be classified according to their clinical and gen- etic features (see next) and, in a small proportion of cases, a recog- nizable metabolic defect can be detected. It is important to make as accurate diagnosis as possible in these disorders for the pur- poses of prognosis, genetic counselling and, occasionally, specific therapy.

section 24 Neurological disorders 5982 Progressive metabolic ataxias Ataxia may be a minor feature of storage and other metabolic neurodegenerative disorders developing in early childhood (see Chapter 24.21). Some enzyme deficiencies that usually give rise to diffuse neurodegenerative disorders, in which ataxia is a feature, developing in infancy or early childhood, include the sphingomyelin lipidoses, metachromatic leukodystrophy, galactosylceramide lipidosis (Krabbe's disease), and the hexosaminidase deficiencies. Also within this group is adrenoleukomyeloneuropathy, a phenotypic variant of adrenoleukodystrophy. This diagnosis is supported by an increase in very long chain fatty acids or by direct genetic analysis of the AMN gene. Although X-linked, approximately 10% of carrier females may manifest neurological abnormalities. The role of diet and dietary supplements (e.g. oleic acid and Lorenzo's oil) remains to be established. Ataxia may be prominent in Niemann–Pick disease type C (juvenile dystonic lipid- osis), combined with a supranuclear gaze palsy. Sphingomyelinase ac- tivity is normal but foamy storage cells are found in the bone marrow. Cholestanolosis (also called cerebrotendinous xanthomatosis or CTX) is a rare autosomal recessive disorder caused by defective bile salt metabolism, due to a deficiency of mitochondrial sterol 27 hydroxylase. It gives rise to ataxia, dementia, spasticity, peripheral neuropathy, cataract, and tendon xanthomata in the second decade of life. Treatment with chenodeoxycholic acid appears to improve neurological function. Various phenotypes that are classifiable as hereditary ataxias have been described in the mitochondrial encephalomyopathies, many of which are associated with a defect of mitochondrial DNA. These include late-onset ataxic disorders are associated (e.g. the Kearns–Sayre syndrome) with such features as dementia, deafness, and peripheral neuropathy. These features overlap with the syn- drome of progressive myoclonic ataxia, which may also be caused by ceroid lipofuscinosis, sialidosis, and Unverricht–Lundborg's disease or so-called Baltic myoclonus. There has been substantial progress in genetic delineation of these syndromes. Acquired metabolic and endocrine disorders causing cerebellar dysfunction Acquired metabolic and endocrine disorders causing cerebellar dys- function include hepatic encephalopathy, pontine and extrapontine myelinolysis related to hyponatraemia, and hypothyroidism. The latter is only very rarely a cause of a cerebellar syndrome in both children and adults. Degenerative disorders The degenerative cerebellar and

spinocerebellar disorders are a com- plex group of diseases, most of which are genetically determined. In some there is an underlying metabolic disorder, and it is important to diagnose these, as there may be important implications for treat- ment and genetic counselling. There has been a rapid growth in our knowledge of the genetic basis of many of the spinocerebellar degenerations. The current phase of research is focussed on how these genes and the abnormal proteins they produce cause cell spe- cific neuropathology. Inherited ataxic disorders can be divided ac- cording to their mode of inheritance (Tables 24.7.4.4 and 24.7.4.5). Most autosomal recessive disorders are of early-onset (less than 20 years), and autosomal dominant disorders are usually of later onset (over 20 years). A recent review of the epidemiology points Table 24.7.4.4 Autosomal recessive ataxias Syndrome Gene defect Clinical notes Friedreich's ataxia GAA repeat (and rarely point mutations
in FRDA gene) Neuropathy, pyramidal signs, skeletal abnormalities, diabetes, and cardiomyopathy ARSACs Sacsin Demyelinating neuropathy and hypertrophied retinal nerve fibre layer (on OCT) Ataxia telangiectasia AT-like disorder ATM hMRE11 Oculomotor apraxia, Mixed movement disorder, humoral immune difficulties, increased cancer risk Cockaynes syndrome CS type A—ERCC8 gene CSA type B—ERCC6 gene 'Cachcectic dwarfism' Mental retardation Pigmentary retinopathy Xeroderma pigmentosum ERCC2 but also probably genetically complex Skin disorder and an increased risk on skin cancer AOA1 Aprataxin Oculomotor apraxia AOA2 Senataxin Oculomotor apraxia Hypogonadism RNF216 Hypogonadotrophic hypogonadism Marinesco–Sjögren syndrome SIL1 on chr 5q31 Cataracts and mental retardation Gillepsie syndrome PAX6 Aniridia Progressive myoclonic ataxia (Ramsay
Hunt syndrome) Genetically complex Epilepsy is common Behr's and related syndromes, e.g. 3-methylglutaconic aciduria type III
(Costeff syndrome) No gene for Behr's yet identified OPA3 gene Optic atrophy, spasticity, and mental retardation Congenital or childhood onset deafness Genetically complex Syndromic diagnosis—likely to have several causes Autosomal recessive late-onset ataxia Heterogeneous Wide clinical variability Onset usually before 20 years of age.

 out that cumulatively these disorders represent a very significant health burden. Autosomal recessive ataxias Friedreich's ataxia This is the most common of the autosomal recessive ataxias (see Table 24.7.4.4) and accounts for at least 50% of cases of hereditary ataxia in most large series reported from Europe and the United States. The prevalence of the disease in these regions is similar, be- tween 1 and 2 per 100 000. The age of onset of symptoms, generally with gait ataxia, is usu- ally between the ages of 8 and 15 years, but onset between 20 and 30, but fulfilling all other diagnostic criteria, have been described. In addition to the progressive ataxia, one finds several vari- able features, including dysarthria and pyramidal tract involve- ment. Initially this latter feature may be mild, with just extensor Table 24.7.4.5b Clinical impact of widely available genetic tests for the ADCAs ADCA type Genetic tests (widely available) Relative contribution to each subclass ADCA I SCA 1, 2, 3, 50% ADCA II SCA7 99% ADCA III SCA6 50% Table 24.7.4.5a Autosomal dominant cerebellar ataxia: clinicogenetic classification. Onset usually over age of 25 years. This is a list of currently identified genes and is divided
by autosomal dominant cerebellar ataxia (ADCA) subtype to facilitate clinical relevance ADCA type Clinical features Genetic loci and chromosomal location Gene ADCA I Cerebellar syndrome plus: Pyramidal signs Supranuclear ophthalmoplegia Extrapyramidal signs Peripheral neuropathy Dementia SCA1 Ataxin 1 CAG SCA2 Ataxin 2 CAG SCA3 Ataxin 3 CAG SCA8 Kelch-like 1 CTG repeat SCA12 PPP2R2B CAG repeat SCA13 KCNC3 point mutations SCA14 PRKCG point mutations SCA15

ITPR1 SCA17 TBP CAG SCA28 AFG3L2 SCA36 Hexanucleotide repeat in NOP56 ADCA II Cerebellar syndrome plus: Pigmentary maculopathy Other signs as ADCA I SCA7 3p12-21.1 Ataxin 7 CAG ADCA III ‘Pure’ cerebellar syndrome Mild pyramidal signs SCA5 SPTBN2 β-III spectrin D SCA6 CACNL 1Aa CAG repeat SCA10 Ataxin 10 ATTCT repeat SCA11 TTBK2 SCA27 FGF14 point mutations Episodic ataxias EA 1 Kv1.1 EA 2 CACNL 1Aa EA3 Locus on 1q42 EA4 No gene identified aka PATX EA5 CACNB4 EA6 SLC1A3 EA8 Plus others yet to be defined Locus 1p36 a SCA6 and CACNL1A are allelic variants.

section 24 Neurological disorders 5984 plantar responses, but after five or more years’ duration of the disease, invariably a pyramidal pattern of weakness in the legs is seen. Eventually this can lead to paralysis. Distal wasting, par- ticularly in the upper limbs, is seen in about 50% of patients with Friedreich’s ataxia. Skeletal abnormalities are also commonly found including scoliosis (85%) and foot deformities, typically pes cavus, in approximately 50% of patients. Additional clinical support for one’s suspicions include optic atrophy which can be seen in 25%; however, it is rare (<5%) for Friedreich’s to produce major visual impairment. Deafness is found in less than 10%, but rather more have impairment of speech discrimination. Nystagmus is seen in only about 20%, but the extraocular movements are nearly always abnormal, with broken-up pursuit, dysmetric saccades, square wave jerks, and failure of fixation suppression of the vestibulo- ocular reflex. Investigation of patients reveals an axonal sensory neuropathy; an abnormal electrocardiogram (ECG) in 65% of patients with wide- spread T-wave inversion. Diabetes mellitus occurs in 10% of patients with Friedreich’s ataxia, and a further 10–20% have impaired glu- cose tolerance. The gene frataxin was identified in 1996. The predominant mutation is a trinucleotide repeat (GAA) in intron 1 of this gene. Expansion of both alleles is found in over 96% of patients. The remaining patients have one expansion and a point mutation in the frataxin gene. This was the first autosomal recessive condi- tion found to be due to a dynamic repeat and it has permitted the introduction of a specific and sensitive diagnostic test, as it is a relatively simple matter to measure the repeat size. On normal chromosomes the number of GAA repeats varies from 7 to 22 units, whereas on disease chromosomes, the range is anything from around 100 to 2000 repeats. The length of the repeat is a determinant of age of onset and therefore to some degree in- fluences the severity in that early-onset tends to progress more rapidly. There has been substantial progress in determining the underlying molecular pathogenesis, principally implicating mitochondrial dys- function, and some hints that manipulation of genomic regulation, eg with nicotinamide may be useful. Other recessive ataxias These are individually rare but increasingly, with widespread adop- tion of whole exome and whole genome sequencing strategies, they are being genetically clarified. However, a few are worth discussing in a little more detail. Ataxic disorders associated with defective DNA repair There are several rare disorders that are characterized at a mo- lecular level by a reduced capacity to repair DNA. The most well- known is ataxia telangiectasia (AT). Characteristically, motor development is often delayed, and ataxia noted at the time of first walking. Growth retardation and delayed sexual development are frequent, and there is mild mental retardation in some cases.
A mixed movement disorder may be seen, often with a combin- ation of ataxia, dystonia, and chorea. The cutaneous telangiectasia of AT tends to develop on the conjunctivae between the ages of 3 and 6 years, but occasionally are inconspicuous or absent in adult life. AT is associated with abnormalities of both humoral and cell- mediated immunity. Direct gene testing is now available.
A rarer but clinically similar disease due to mutations in hMRE11 has been identified and is termed AT-like disorder. Clinically related conditions xeroderma pigmentosum and Cockayne’s syndrome (see Table 24.7.4.4) are now broadly con- sidered disorders of excision repair (see Rapin 2013).

Ataxia associated with oculomotor apraxia. There are two genetically distinct but clinically similar disorders associated with the distinctive feature of oculomotor apraxia types 1 and 2. Oculomotor apraxia represents a deficit of the voluntary saccadic system and should be suspected in the presence of head thrusts or synkinetic blinking which are used to help initiate a vol- untary saccade. AOA1, was shown to be due to mutations in a gene called aprataxin. It is characterized by the association of ataxia with chorea early in the disease course, oculomotor apraxia, peripheral neuropathy, and variable but mild learning difficulties. MRI reveals cerebellar atrophy and serum analysis may show hypercholesterol- aemia and hypoalbuminaemia. A second condition AOA2 is very similar clinically and also over- laps with the AT phenotype (see earlier). Mutations in senataxin have been shown to cause this syndrome. α-fetoprotein is elevated in virtually all cases and is therefore a useful screen for this disorder. It also appears it may be more common than either AT of AOA1 ac- counting for approximately 8% of autosomal recessive ataxia. The other autosomal recessive ataxias are all individually rare and are listed in Table 24.7.4.4. Testing for ATM, aprataxin, and senataxin is now possible in a specialized lab. See Le Ber and colleagues (2012) for a recent review. The finding of mutations in a gene called sacsin as the cause of a complicated form of autosomal recessive ataxia (ARSACS) proved illuminating. Hitherto it had been appreciated as an extremely rare form originating in small community in Quebec. However, once the gene was identified it became clear that along with senataxin, it was second only to FRDA in terms of frequency and is found all over the world. A recent review by Pilliot et al. provides useful in- sights into the clinical features and diagnostic criteria. It is worth thinking of ARSACS in cases of young onset ataxia in which one finds a demyelinating neuropathy and optical coherence tomograph (OCT) can be useful in demonstrating retinal layer hypertrophy (Fig. 24.7.4.1).
Autosomal dominant cerebellar ataxias The autosomal dominant cerebellar ataxias (ADCAs) are a clinically and genetically complex group of neurodegenerative disorders (see Table 24.7.4.5a, b). ADCA type I is characterized by a progressive cerebellar ataxia and is variably associated with other extracerebellar neurological features such as ophthalmoplegia, optic atrophy, per- ipheral neuropathy, pyramidal, and extrapyramidal signs. The presence and severity of these signs is, in part, dependent on the duration of the disease. Mild or moderate dementia may occur, but it is usually not a prominent early feature. ADCA type II is clinically distinguished from the ADCA type I by the presence of pigmentary macular dystrophy see Fig. 24.7.4.2, whereas ADCA type III is a relatively ‘pure’ cerebellar syndrome and generally starts at a later age. This clinical classification is still useful, despite the tremendous improvements in our understanding of the genetic basis (see next), because it provides a framework which can be used in the clinic and helps direct the genetic evaluation.

 The genetic loci causing the dominant ataxias are given the acronym SCA (spino-cerebellar ataxia). At the time of publica- tion there are over 30 SCA loci identified. However, with the dis- covery of the genes it becomes apparent that some of these are duplicates and there are yet still more to be found. In general clin- ical practice, five of these genes are established (SCAs 1, 2, 3, 6, and 7). Interestingly they are all caused by a similar mutational mechanism, an expansion of an exonic CAG repeat. The resultant proteins all possess an expanded polyglutamine tract and there are now at least eight conditions caused by these expansions. Other types of ADCA are rare and mutation testing is only available for a small number of these.
Idiopathic degenerative late-onset ataxias About two-thirds of cases of degenerative ataxia developing over the age of 20 years are isolated cases, and they represent a signifi- cant clinical problem; it is difficult even to know how to label them. The literature is confusing, mixing

pathological terms such as olivo- ponto-cerebellar atrophy with clinical terms; the author prefers to use the term ‘idiopathic late-onset cerebellar ataxia’ (ILOCA). A pro- portion of patients in this group, progress to develop the features of multiple system atrophy (MSA) (see Chapter 24.7.3). These patients may have or develop facial impassivity and extrapyramidal rigidity, while others present with features of autonomic failure such as pos- tural hypotension, impotence, bladder dysfunctions, and a fixed car- diac rate. A cerebellar presentation occurs in about 30% of patients with MSA. The distinction of idiopathic late-onset cerebellar ataxia from MSA may, therefore, be difficult clinically at presentation. Most patients with idiopathic late-onset cerebellar ataxia lose the ability to walk independently between 5 and 20 years after onset, and lifespan is slightly shortened by immobility. Those who go on to develop MSA have a particularly poor prognosis. Investigations, apart from those excluding acquired causes of cerebellar degener- ation such as malignancy and hypothyroidism, tend to be unhelpful. Electrophysiological evidence of a sensory peripheral neuropathy is found in about 50% of cases, which can be a useful pointer to the presence of a degenerative multisystem disorder. CT or MRI scan may show cerebellar and brain stem atrophy, or pure cerebellar at- rophy. The prognosis is worse in patients with clinical and radio- logical evidence of brain stem involvement, compared to those with Fig. 24.7.4.1 The retinal hypertrophy almost pathognomonic of autosomal recessive spastic ataxia of Charlevoix Sagueney (ARSACs). Courtesy of Dr Fion Bremner National Hospital London. Fig. 24.7.4.2 The distinctive maculopathy associated with SCA7 (clinically synonymous with autosomal dominant cerebellar ataxia (ADCA) II).

section 24 Neurological disorders 5986 a pure cerebellar syndrome and cerebellar atrophy alone on MRI (Klockgether et al., 1990). The role of gliadin sensitivity in producing a chronic progressive ataxia (and indeed other neurological conditions), either as part of coeliac disease or as a purely neurological phenotype is still debated. A recent meta-analysis in children did not identify a significant risk above the general population. Over the last decade a newly recognized condition has been shown to explain a small minority of cases. Usually male patients in mid to late life develop a progressive phenotype of ataxia and tremor in association with an intermediate expansion in the fragile X gene. This has been termed FXTAS (Fragile X Tremor Ataxia Syndrome). A recent review by Hagerman and Hagerman (2015) provides useful details of the core features and variable phenoptypes associated with this mutation. FURTHER READING Baloh RW (2012). Episodic ataxias 1 and 2. Handb Clin Neurol, 103, 595–602. Campuzano V, et al. (1996). Friedreich’s ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science, 271, 1423–27. Cavalier L, et al. (1998). Ataxia with isolated vitamin E deficiency: heterogeneity of mutations and phenotypic variability in a large number of families. Am J Hum Genet, 62, 301–10. de Michele G, et al. (1989). Late onset recessive ataxia with Friedreich’s disease phenotype. J Neurol Neurosurg Psychiatry, 52, 1398–403. Enevoldson PG, Sanders MD, Harding AE (1994). Autosomal dom- inant cerebellar ataxia with pigmentary macular dystrophy: a clin- ical and genetic study of eight families. Brain, 117, 445–60. Everett CM, Wood NW (2004). Trinucleotide repeats and neuro degenerative disease. Brain, 127, 2385–405. Fearnley JM, Stevens JM, Rudge P (1995). Superficial siderosis of the central nervous system. Brain, 118, 1051–66. Gilman S, et al. (2008). Second consensus statement on the diagnosis of multiple system atrophy. Neurology, 71, 670–6. Hadjivassiliou M, et al. (2003). Gluten ataxia in perspective: epidemi- ology, genetic susceptibility and clinical characteristics. Brain, 126, 685–91. Hagerman PJ, Hagerman RJ (2015). Fragile X-associated tremor/ ataxia syndrome. Ann N Y Acad Sci, 1338, 58–70. Harding AE (1994). The hereditary ataxias and related disorders. Churchill Livingstone, Edinburgh. Jacquemont S, et al. (2004). Penetrance of the fragile X-associated tremor/ataxia syndrome in a premutation carrier population. JAMA, 291, 460–9. Kälviäinen R (2015). Progressive myoclonus epilepsies. Semin

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